

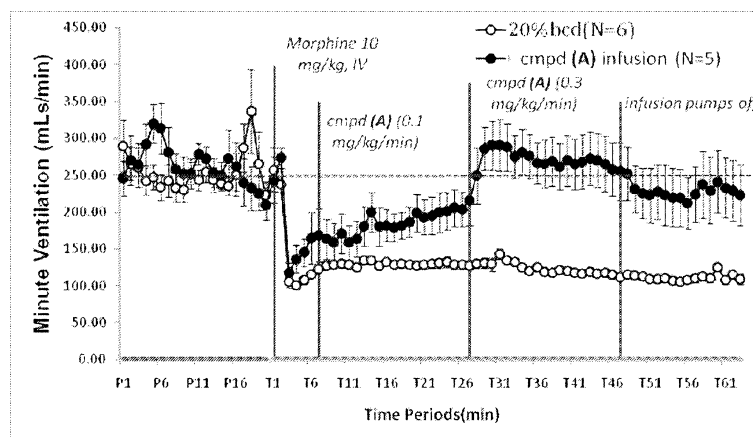
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6 February 2014(54) Title: NOVEL COMPOUNDS AND COMPOSITIONS FOR TREATMENT OF BREATHING CONTROL DISORDERS OR
DISEASES**Fig. 1**(57) **Abstract:** The present invention includes compositions that are useful in the treatment of breathing control diseases or disorders in a subject in need thereof. The present invention also includes a method of treating a respiratory disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a pharmaceutical formulation of the invention. The present invention further includes a method of preventing destabilization or stabilizing breathing rhythm in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a pharmaceutical formulation of the invention.

TITLE OF THE INVENTION

Novel Compounds and Compositions for Treatment of Breathing Control Disorders or Diseases

5

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to U.S. Patent Application No. 13/482,837, filed May 29, 2012, which is a continuation-in-part of and claims priority to U.S. Patent Application No. 13/306,349, filed November 29, 2011, which is
10 entitled to priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Applications No. 61/417,777, filed November 29, 2010, and No. 61/494,268, filed June 7, 2011, all of which are hereby incorporated by reference in their entireties herein.

BACKGROUND OF THE INVENTION

15 Normal control of breathing is a complex process that involves, in part, the body's interpretation and response to chemical stimuli such as carbon dioxide, pH and oxygen levels in blood, tissues and the brain. Breathing control is also affected by other factors such as wakefulness (i.e., whether the patient is awake or sleeping), emotion, posture and vocalization. Within the brain medulla, there are respiratory
20 control centers that interpret various feedforward and feedback signals that affect respiration and issues commands to the muscles that perform the work of breathing. Key muscle groups are located in the abdomen, diaphragm, pharynx and thorax. Sensors located centrally and peripherally then provide input to the brain's central respiration control areas that enables response to changing metabolic requirements.

25 For example, ventilation sufficient to meet the body's metabolic needs is maintained primarily by the body's rapid response to changes in carbon dioxide levels (CO₂). Increased CO₂ levels signal the body to increase breathing rate and depth, resulting in higher blood oxygen levels and subsequent lower blood CO₂ levels. Conversely, low CO₂ levels can result in periods of hyponea (decreased breathing) or,
30 in the extreme case, apnea (no breathing) since the stimulation to breathe is diminished. This is what happens when a person hyperventilates.

There are many diseases in which loss of normal breathing control is a primary or secondary feature of the disease. Examples of diseases with a primary loss of breathing control are apneas (central, mixed or obstructive; where the breathing

repeatedly stops for 10 to 60 seconds) and congenital central hypoventilation syndrome. Secondary loss of breathing control may be due to chronic cardio-pulmonary diseases (e.g., heart failure, chronic bronchitis, emphysema, and impending respiratory failure), excessive weight (e.g., obesity-hypoventilation syndrome), certain drugs (e.g., anesthetics, sedatives, anxiolytics, hypnotics, alcohol, and narcotic analgesics and/or factors that affect the neurological system (e.g., stroke, tumor, trauma, radiation damage, and ALS). In chronic obstructive pulmonary diseases where the body is exposed to chronically high levels of carbon dioxide, the body adapts to the lower pH by a kidney mediated retention of bicarbonate, which has the effect of partially neutralizing the CO₂/pH respiratory stimulation. Thus, the patient is unable to mount a normal ventilatory response to changes in metabolic demand.

Sleep disordered breathing is an example of where abnormalities in the control of breathing lead to a serious and prevalent disease in humans. Sleep apnea is characterized by frequent periods of no or partial breathing. Key factors that contribute to these apneas include anatomical factors (such as obesity), decreased hypercapnic and hypoxic ventilatory responses (e.g., decreased response to high carbon dioxide and low oxygen levels, respectively) and loss of “wakefulness” (i.e., drive to pharyngeal dilator muscles). Apneic events result in hypoxia (and the associated oxidative stress) and eventually severe cardiovascular consequences (high blood pressure, stroke, heart attack).

Estimates for U.S. individuals afflicted with conditions wherein there is compromised respiratory control include sleep apneas (15-20 millions); obesity-hypoventilation syndrome (5-10 millions); chronic heart disease (5 millions); chronic obstructive pulmonary disease (COPD)/chronic bronchitis (10 millions); drug-induced hypoventilation (2-5 millions); and mechanical ventilation weaning (0.5 million).

There is a need in the art for novel chemical compounds that can be used to restore all or part of the body's normal breathing control system in response to changes in CO₂ and/or oxygen, with minimal side effects. Such compounds would be of benefit in decreasing the incidence and severity of breathing control disturbances. The present invention addresses and meets these needs.

BRIEF SUMMARY OF THE INVENTION

The invention includes a composition comprising at least one compound selected from the group consisting of: N-(2,4-bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine (CLXXII), N-(2,4,6-tris-*n*-propylamino)-[1,3,5]triazine (CLXXIII), N-(2,4,6-tris-*n*-propylamino)-1,3-pyrimidine (CLXXIV), N-(2,4-bis-*n*-propylamino)-N-(6-*i*-propylamino)-1,3-pyrimidine (CLXXV), a salt thereof, and any combinations thereof.

In one embodiment, the salt is hydrogen sulfate, hydrochloride, phosphate, hydrogen phosphate or dihydrogen phosphate. In another embodiment, the composition further comprises at least one pharmaceutically acceptable carrier.

The invention also includes a method of preventing or treating a breathing control disorder or disease in a subject in need thereof. The method comprises administering to the subject an effective amount of a pharmaceutical formulation comprising at least one pharmaceutically acceptable carrier and at least one compound selected from the group consisting of: N-(2,4-bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine (CLXXII), N-(2,4,6-tris-*n*-propylamino)-[1,3,5]triazine (CLXXIII), N-(2,4,6-tris-*n*-propylamino)-1,3-pyrimidine (CLXXIV), N-(2,4-bis-*n*-propylamino)-N-(6-*i*-propylamino)-1,3-pyrimidine (CLXXV), a salt thereof, and any combinations thereof.

In one embodiment, the breathing control disorder or disease is selected from the group consisting of respiratory depression, sleep apnea, apnea of prematurity, obesity-hypoventilation syndrome, primary alveolar hypoventilation syndrome, dyspnea, hypoxia, and hypercapnia. In another embodiment, the respiratory depression is caused by an anesthetic, a sedative, an anxiolytic agent, a hypnotic agent, alcohol or a narcotic. In yet another embodiment, the subject is further administered a composition comprising at least one additional compound useful for treating the breathing control disorder or disease. In yet another embodiment, the at least one additional compound is selected from the group consisting of acetazolamide, almitrine, theophylline, caffeine, methyl progesterone, a serotonergic modulator, a cannabinoid and an ampakine. In yet another embodiment, the formulation is administered in conjunction with the use of a mechanical ventilation device or positive airway pressure device on the subject. In yet another embodiment, the subject is a mammal. In yet another embodiment, the mammal is a human. In yet another embodiment, the formulation is administered to the subject by

an inhalational, topical, oral, buccal, rectal, vaginal, intramuscular, subcutaneous, transdermal, intrathecal, intraperitoneal, intrathoracic, intrapleural or intravenous route.

The invention also includes a method of preventing destabilization or stabilizing breathing rhythm in a subject in need thereof. The method comprising administering to the subject an effective amount of a pharmaceutical formulation comprising at least one pharmaceutically acceptable carrier and at least one compound selected from the group consisting of: N-(2,4-bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine (CLXXII), N-(2,4,6-tris-*n*-propylamino)-[1,3,5]triazine (CLXXIII), N-(2,4,6-tris-*n*-propylamino)-1,3-pyrimidine (CLXXIV), N-(2,4-bis-*n*-propylamino)-N-(6-*i*-propylamino)-1,3-pyrimidine (CLXXV), a salt thereof, and any combinations thereof.

In one embodiment, the destabilization is associated with a breathing control disorder or disease selected from the group consisting of respiratory depression, sleep apnea, apnea of prematurity, obesity-hypoventilation syndrome, primary alveolar hypoventilation syndrome, dyspnea, hypoxia, and hypercapnia. In another embodiment, the respiratory depression is caused by an anesthetic, a sedative, an anxiolytic agent, a hypnotic agent, alcohol or a narcotic. In yet another embodiment, the subject is further administered a composition comprising at least one additional compound useful for treating the breathing control disorder or disease. In yet another embodiment, the at least one additional compound is selected from the group consisting of acetazolamide, almitrine, theophylline, caffeine, methyl progesterone, a serotonergic modulator, a cannabinoid and an ampakine. In yet another embodiment, the formulation is administered in conjunction with the use of a mechanical ventilation device or positive airway pressure device on the subject. In yet another embodiment, the subject is a mammal. In yet another embodiment, the mammal is a human. In yet another embodiment, the formulation is administered to the subject by an inhalational, topical, oral, buccal, rectal, vaginal, intramuscular, subcutaneous, transdermal, intrathecal, intraperitoneal, intrathoracic, intrapleural or intravenous route.

The invention also includes a composition comprising N-(4,6-bis-*n*-propylamino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV) or a salt thereof, wherein 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol (CLXXVIII) is present at

a level equal to or lower than about 1% (w/w) with respect to (XXXV) or the salt thereof.

In one embodiment, 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol (CLXXVIII) is present at a level equal to or lower than about 0.5% (w/w) with respect to (XXXV) or the salt thereof. In another embodiment, 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol (CLXXVIII) is present at a level equal to or lower than about 0.3% (w/w) with respect to (XXXV) or the salt thereof. In yet another embodiment, 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol (CLXXVIII) is present at a level equal to or lower than about 0.2% (w/w) with respect to (XXXV) or the salt thereof. In yet another embodiment, 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol (CLXXVIII) is present at a level equal to or lower than about 0.15% (w/w) with respect to (XXXV) or the salt thereof. In yet another embodiment, 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol (CLXXVIII) is present at a level equal to or lower than about 0.1% (w/w) with respect to (XXXV) or the salt thereof. In yet another embodiment, 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol (CLXXVIII) is essentially absent from the composition.

The invention also includes a composition comprising N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV) or a salt thereof, further comprising a buffer and a liquid carrier.

In one embodiment, the salt of (XXXV) is the hydrogen sulfate salt (XXXVI). In another embodiment, the composition further comprises citric acid. In yet another embodiment, the pH of the composition is adjusted with a base. In yet another embodiment, the base comprises sodium hydroxide. In yet another embodiment, the liquid carrier comprises water. In yet another embodiment, the pH of the composition ranges from about 2.5 to about 6. In yet another embodiment, the pH of the composition ranges from about 2.5 to about 5. In yet another embodiment, the pH of the composition ranges from about 3 to about 4. In yet another embodiment, the concentration of (XXXV) or the salt thereof in the composition is about 1-10 mg/mL. In yet another embodiment, the concentration of (XXXV) or the salt thereof in the composition is about 5-10 mg/mL. In yet another embodiment, the concentration of (XXXV) or the salt thereof in the composition is about 10 mg/mL. In yet another embodiment, the composition comprises less than 0.5% (w/w) (CLXXVIII) with respect to (XXXV). In yet another embodiment, less than 0.5% (w/w) of N-(4,6-Bis-*n*-propylamino)-[1,3,5]-triazin-2-ol (CLXXVIII) with respect to

(XXXV) forms over a six-month period of storage of the composition at 2-8°C. In yet another embodiment, wherein less than 0.5% (w/w) of N-(4,6-Bis-*n*-propylamino)-[1,3,5]-triazin-2-ol (CLXXVIII) with respect to (XXXV) forms over a twelve-month period of storage of the composition at 2-8°C. In yet another
5 embodiment, less than 0.5% (w/w) of N-(4,6-Bis-*n*-propylamino)-[1,3,5]-triazin-2-ol (CLXXVIII) with respect to (XXXV) forms over an eighteen-month period of storage of the composition at 2-8°C. In yet another embodiment, less than 0.5% (w/w) of N-(4,6-Bis-*n*-propylamino)-[1,3,5]-triazin-2-ol (CLXXVIII) with respect to (XXXV) forms over a twenty-four-month period of storage of the composition at 2-8°C.

10 The invention also includes a crystalline free base of N-(4,6-Bis-*n*-propylamino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV), Form A, with a XRPD spectrum as per Figure 22.

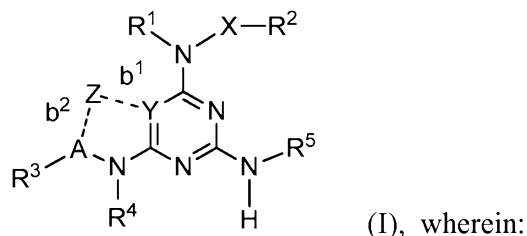
The invention also includes at least one crystalline salt of N-(4,6-Bis-*n*-propylamino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV) selected
15 from the group consisting of: crystalline hydrogen sulfate salt (XXXVI) Form A, with a XRPD spectrum as per Figure 14; crystalline hydrogen sulfate salt (XXXVI) comprising a mixture of Form A and Form B, with a XRPD spectrum as per Figure 23; crystalline hydrogen sulfate salt (XXXVI) Form C, with a XRPD spectrum as per Figure 24; crystalline hydrogen sulfate salt (XXXVI) Form D, with a XRPD spectrum
20 as per Figure 25; crystalline hydrogen sulfate salt (XXXVI) comprising a mixture of Form A and Form D, with a XRPD spectrum as per Figure 26; crystalline phosphoric acid salt (CLXXX) Form A, with a XRPD spectrum as per Figure 27; crystalline phosphoric acid salt (CLXXX) Form C, with a XRPD spectrum as per Figure 28; crystalline phosphoric acid salt (CLXXX) comprising a mixture of Form A and Form
25 B, with a XRPD spectrum as per Figure 29; crystalline phosphoric acid salt (CLXXX) comprising a mixture of Form C and Form D, with a XRPD spectrum as per Figure 30; crystalline phosphoric acid salt (CLXXX) comprising a mixture of Form C and Form E, with a XRPD spectrum as per Figure 31; and any mixtures thereof.

The invention also includes a salt of N-(4,6-Bis-*n*-propylamino)-
30 [1,3,5]triazin-2-yl)-hydroxylamine (XXXV), comprising approximately one mole equivalent of sulfuric acid. In one embodiment, the salt further comprises one mole equivalent of water.

The invention also includes a salt of N-(4,6-Bis-*n*-propylamino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV), comprising at least one

mole equivalent of phosphoric acid. In one embodiment, the salt comprises about one mole equivalent of phosphoric acid.

The invention also includes a method of reducing or minimizing the open channel fraction of the potassium maxi-K or BK channel in a subject in need thereof. The method comprises administering to the subject an effective amount of a pharmaceutical formulation comprising at least one pharmaceutically acceptable carrier and at least one compound of formula (I):

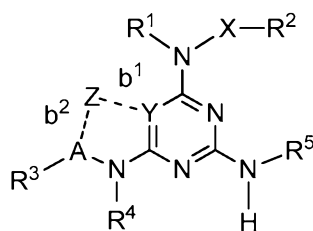


R^1 and R^2 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl; or R^1 and R^2 combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl; R^3 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-NR^1R^2$, $-C(O)OR^1$, acyl, or aryl; R^4 is H, alkyl, or substituted alkyl; R^5 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-OR^1$, $-NR^1R^2$, $-C(O)OR^1$, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, or substituted heterocyclic; or R^3 and R^5 combine as to form a biradical selected from the group consisting of 3,6,9-trioxa-undecane-1,11-diyl and 3,6-dioxa-octane-1,8-diyl; R^6 is H, alkyl, substituted alkyl or alkenyl; X is a bond, O or NR^4 ; and, Y is N, CR^6 or C; wherein:

if Y is N or CR^6 , then bond b^1 is nil and: (i) Z is H, bond b^2 is a single bond, and A is CH; or, (ii) Z is nil, bond b^2 is nil, and A is a single bond; and, if Y is C, then bond b^1 is a single bond, and: (i) Z is CH_2 , bond b^2 is a single bond, and A is CH; or, (ii) Z is CH, bond b^2 is a double bond, and A is C; or a salt thereof.

The invention also includes a method of inhibiting the TASK-1 (KCNK3) channel in a subject in need thereof. The method comprises administering

to the subject an effective amount of a pharmaceutical formulation comprising at least one pharmaceutically acceptable carrier and at least one compound of formula (I):

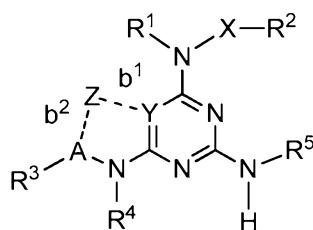


(I), wherein:

- R^1 and R^2 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl; or R^1 and R^2 combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl; R^3 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-NR^1R^2$, $-C(O)OR^1$, acyl, or aryl; R^4 is H, alkyl, or substituted alkyl; R^5 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-OR^1$, $-NR^1R^2$, $-C(O)OR^1$, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, or substituted heterocyclic; or R^3 and R^5 combine as to form a biradical selected from the group consisting of 3,6,9-trioxa-undecane-1,11-diyl and 3,6-dioxa-octane-1,8-diyl; R^6 is H, alkyl, substituted alkyl or alkenyl; X is a bond, O or NR^4 ; and, Y is N, CR^6 or C; wherein:

- if Y is N or CR^6 , then bond b^1 is nil and: (i) Z is H, bond b^2 is a single bond, and A is CH; or, (ii) Z is nil, bond b^2 is nil, and A is a single bond; and, if Y is C, then bond b^1 is a single bond, and: (i) Z is CH_2 , bond b^2 is a single bond, and A is CH; or, (ii) Z is CH, bond b^2 is a double bond, and A is C; or a salt thereof.

- The invention also includes a method of increasing minute ventilation in a subject in need thereof. The method comprises administering to the subject an effective amount of a pharmaceutical formulation comprising at least one pharmaceutically acceptable carrier and at least one compound of formula (I):



(I), wherein:

- R^1 and R^2 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl; or R^1 and R^2 combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl; R^3 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-NR^1R^2$, $-C(O)OR^1$, acyl, or aryl; R^4 is H, alkyl, or substituted alkyl; R^5 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-OR^1$, $-NR^1R^2$, $-C(O)OR^1$, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, or substituted heterocyclic; or R^3 and R^5 combine as to form a biradical selected from the group consisting of 3,6,9-trioxa-undecane-1,11-diyl and 3,6-dioxa-octane-1,8-diyl; R^6 is H, alkyl, substituted alkyl or alkenyl; X is a bond, O or NR^4 ; and, Y is N, CR^6 or C; wherein:

if Y is N or CR^6 , then bond b^1 is nil and: (i) Z is H, bond b^2 is a single bond, and A is CH; or, (ii) Z is nil, bond b^2 is nil, and A is a single bond; and,

- if Y is C, then bond b^1 is a single bond, and: (i) Z is CH_2 , bond b^2 is a single bond, and A is CH; or, (ii) Z is CH, bond b^2 is a double bond, and A is C; or a salt thereof.

In one embodiment, the compound of formula (I) is selected from the group consisting of: N-(4,6-Bis-methylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-ethylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-Cyclopropylmethyl)-N-(6-*n*-propylamino) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-Ethylamino)-N-(6-*n*-propylamino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2-methylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2,2-dimethylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2,2-dimethylpropylamino))[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-

Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-(Methoxy(methyl)amino)-6-(*n*-propylamino)-1,3,5-triazin-2-yl)propionamide, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-methyl-hydroxylamine, O-Allyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine, 6-(Methoxy(methyl)amino)-N²-propyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine, O-Benzyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-isopropyl-hydroxylamine, 6-[1,2]Oxazinan-2-yl-N,N'-dipropyl-[1,3,5]triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-N-methyl-hydroxylamine, O-Benzyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-hydroxylamine, 6-((Benzyloxy)(isopropyl) amino)-N²,N⁴-dipropyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-O-isopropyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isobutyl-N-methyl-hydroxylamine, 6-(Methyl(thiophen-2-ylmethoxy)amino)-N²,N⁴-dipropyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-cyclopropylmethyl-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-ethyl-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-(2,2-difluoro-ethyl)-hydroxylamine, 4-N-(2-Dimethylaminoethyl)amino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4-N-(3-(1-N-Methylimidazol-2-yl)-propyl)-amino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4-N-(1-N-Methylimidazol-2-yl)-methylamino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-(N-(2-dimethylaminoethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-(N-(pyridin-4-yl-methyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-[N-(3-methoxy-*n*-propyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-[N-(tetrahydropyran-4-yl-methyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(5,8,11-Trioxa-2,14,16,18,19-pentaazabicyclo[13.3.1]nonadeca-1(18),15(19),16(17)-trien-17-yl)-N,O-dimethylhydroxylamine, 2,6-Bis-(N-*n*-propylamino)-[1,3]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N',N'-dimethylhydrazine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-N'-methylhydrazine, 2-(*n*-Propyl)amino-4-(*i*-propylamino-7-methyl-pyrrolidino[2,3-

d]pyrimidine, 2-(*n*-Propyl)amino-4-dimethylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine, 2-(*n*-Propyl)amino-4-methylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine, 2-(*n*-Propyl)amino-4-(*i*-propyl)amino-7-*i*-propyl-pyrrolidino[2,3-d]pyrimidine, 2,4-Bis-(*n*-propyl)amino-7H-pyrrolidino[2,3-d]pyrimidine, 2-(*n*-Propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-methyl-pyrrolidino[2,3-d]pyrimidine, 8-(7-Methyl-2-(*n*-propylamino)-pyrrolidino[2,3-d]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol, N-(2-Propylamino-7H-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine, N-Methyl-N-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine, N,N-Dimethyl-N'-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine, N-(2,4-Bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine, N-(2,4,6-Tris-*n*-propylamino)-[1,3,5]triazine, N-(2,4,6-Tris-*n*-propylamino)-1,3-pyrimidine, N-(2,4-Bis-*n*-propylamino)-N-(6-*i*-propylamino)-1,3-pyrimidine, a salt thereof and mixtures thereof.

20 In one embodiment, the compound of formula (I) is selected from the group consisting of: N-(4,6-Bis-*n*-propylamino-1,3,5]triazin-2-yl)-O-methyl-hydroxylamine; N-(4,6-Bis-*n*-propylamino-1,3,5]triazin-2-yl)-N',N'-dimethylhydrazine; N-(2,4-Bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine; N-[(2,6-Bis-*n*-propylamino)-pyrimidin-4-yl]-N,O-dimethyl-hydroxylamine; N,N-Dimethyl-N'-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine; a salt thereof and mixtures thereof.

In one embodiment, the compound of formula (I) is N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, or a salt thereof.

30 In one embodiment, the pharmaceutical formulation is administered via intravenous infusion. In another embodiment, the infusion dose of the pharmaceutical formulation is at least about 0.016 mg/kg/min. In yet another embodiment, the infusion dose of the pharmaceutical formulation is about 0.016 mg/kg/min. In yet another embodiment, the infusion dose of the pharmaceutical composition produce plasma concentrations of at least about 726 ng/mL in the

subject. In yet another embodiment, the subject is a mammal. In yet another embodiment, the mammal is human.

BRIEF DESCRIPTION OF THE DRAWINGS

5 For the purpose of illustrating the invention, there are depicted in the drawings certain embodiments of the invention. However, the invention is not limited to the precise arrangements and instrumentalities of the embodiments depicted in the drawings.

Figure 1 is a graph illustrating results of plethysmography experiments
10 which monitored minute ventilation in the opioid-treated rat upon administration of Compound (XXXVI) [labeled as cmpd (A)].

Figure 2, comprising Figures 2A-B, illustrates arterial blood gas analysis results for administration of Compound (XXXVI) [labeled as cmpd (A)] in the opioid-treated rat. Figure 2A – PaCO₂ (mmHg); Figure 2B – SaO₂ (%).

15 Figure 3 is a graph illustrating results of plethysmography experiments monitoring minute ventilation in the rat upon administration of Compound (XXXVI) [labeled as cmpd (A)] under conditions of hypoxia.

Figure 4 is a graph illustrating end-tidal CO₂ and minute ventilation in the opioid-treated monkey upon administration of Compound (XXXVI) [labeled as
20 cmpd (A)].

Figure 5 is a graph illustrating the dose-dependent effect of Compound (XXXVI) [labeled as cmpd (A)] and Compound (L) [labeled as cmpd (B)] on minute ventilation, in terms of maximum peak response, in the rat.

Figure 6 is a graph illustrating the dose-dependent effect of Compound
25 (XXXVI) [labeled as cmpd (A)] and Compound (CXXI) [labeled as cmpd (C)] on minute ventilation, in terms of maximum peak response, in the rat.

Figure 7, comprising Figures 7A-D, illustrates the dose-dependent effect of Compound (L) [labeled as cmpd (B)] on blood gases and pH in the opioid-treated rat. Figure 7A – pH; Figure 7B – SaO₂; Figure 7C – pO₂; Figure 7D –
30 pCO₂.

Figure 8, comprising Figures 8A-D, illustrates the dose-dependent effect of Compound (CXLII) [labeled as cmpd (D)] on blood gases and pH in the opioid-treated rat. Figure 8A – pO₂; Figure 8B – SaO₂; Figure 8C – pCO₂; Figure 8D – pH.

Figure 9 is a graph illustrating the effect of Compound (CXLII) [labeled as cmpd (D)] in the minute ventilation of the opioid-treated rat.

Figure 10 illustrates the ^1H -NMR spectrum for Compound (XXXVI) in DMSO- d_6 at 25°C.

5 Figure 11 illustrates the ^{13}C -NMR spectrum for Compound (XXXVI) in DMSO- d_6 at 25°C.

Figure 12 illustrates the FTIR spectrum for Compound (XXXVI).

Figure 13 illustrates the thermal analysis by DSC of N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI).

Figure 14 illustrates the X-ray diffraction spectrum of Compound (XXXVI) Form A (hydrogen sulfate salt Form A).

Figure 15 is a graph illustrating the effect of Compound (XXXVI) on reversing the effects of midazolam on minute ventilation (MV) in the rat.

15 Figure 16 is a graph illustrating the effect of Compound (XXXVI) on reversing the effects of midazolam on tidal volume (TV) in the rat.

Figure 17 is a graph illustrating the effect of Compound (XXXVI) on reversing the effects of midazolam on respiratory frequency (f) in the rat.

Figure 18 is a graph illustrating the effect of Compound (XXXVI) infusion on the minute volume response to acute hypercapnia (3% CO_2).

Figure 19A is a graph illustrating the effect of pH on aqueous solubility of Compound (XXXV) at ambient temperature. Figure 19B is a graph illustrating the effect of pH on aqueous solubility of Compound (XXXV) at ambient temperature

25 Figure 20A is a graph illustrating the effect of pH on degradation of Compound (XXXV) at pH 2-6. Figure 20B is a graph illustrating the effect of pH on degradation of Compound (XXXV) at pH 2-3.6.

Figure 21 is a graph illustrating the formation rate of Compound (CLXXVIII) from Compound (XXXV) in solution at 2-8°C, pH 3-4.

30 Figure 22 is a graph illustrating the X-ray powder diffraction pattern of the free base of Compound (XXXV)

Figure 23 is a graph illustrating the X-ray powder diffraction spectrum of a mixture of Compound (XXXVI) Form A and Compound (XXXVI) Form B.

Figure 24 is a graph illustrating the X-ray powder diffraction spectrum of Compound (XXXVI) Form C.

Figure 25 is a graph illustrating the X-ray powder diffraction spectrum of Compound (XXXVI) Form D.

5 Figure 26 is a graph illustrating the X-ray powder diffraction spectrum of a mixture of Compound (XXXVI) Form A and Compound (XXXVI) Form D.

Figure 27 is a graph illustrating the X-ray powder diffraction spectrum of Compound (CLXXX) Form A.

Figure 28 is a graph illustrating the X-ray powder diffraction spectrum
10 of Compound (CLXXX) Form C.

Figure 29 is a graph illustrating the X-ray powder diffraction spectrum of a mixture of Compound (CLXXX) Form A and Compound (CLXXX) Form B.

Figure 30 is a graph illustrating the X-ray powder diffraction spectrum of a mixture of Compound (CLXXX) Form C and Compound (CLXXX) Form D.

15 Figure 31 is a graph illustrating the X-ray powder diffraction spectrum of a mixture of Compound (CLXXX) Form C and Compound (CLXXX) Form E.

Figure 32, comprising Figures 32A-D, are graphs illustrating the effect of Compound (XLII) on respiratory rate (Figure 32A), tidal volume (Figure 32B), minute volume (Figure 32C) and 5 min average change in minute volume (Figure
20 32D) respectively, in rat.

Figure 33, comprising Figures 33A-D, are graphs illustrating the effect of Compound (CLXXII) on respiratory rate (Figure 33A), tidal volume (Figure 33B), minute volume (Figure 33C) and 5 min average change in minute volume (Figure 33D) respectively, in rat.

25 Figure 34, comprising Figures 34A-C, illustrates the effect of BK channel activity in response to Compound (XXXV) at a concentration of 1 μ M. Figure 34A: sample recordings of channel activity in control conditions and with 1 μ M (XXXV). Arrow, closed state. Figure 34B: all points histogram obtained from 1 min of recording in control condition. Figure 34C: all points histogram obtained
30 from 1 min of recording with 1 μ M (XXXV). Patch ID: C 05 SP 101008_0000.

Figure 35 illustrates the design of study GAL-021-101: infusion rates and duration by study period and group (cohort). The dose levels that were pooled for PD analyses are delineated on the left side.

Figure 36 is an illustrative design diagram of respiratory depression Proof-of-Concept study (GAL-021-104).

Figure 37 is a graph illustrating tidal volume during first 2 hour after starting the infusion.

5 Figure 38, comprising Figures 38A-D, is a set of graphs illustrating the integrated percent change from baseline during the first hour (0-1h) and first 2 hours (0-2h) after starting the infusion for minute ventilation (Figure 38A), end tidal CO₂ (Figure 38B), respiratory rate (Figure 38C), and tidal volume (Figure 38D) in the initial clinical study (GAL-021-101). Data from the first hour of period 9 (0.96
10 mg/kg/h) was pooled with data from similar infusion rate subjects in groups 6 and 7 for the 0-1h assessments.

Figure 39, comprising Figures 39A-D, is a set of graphs illustrating integrated percent change from baseline during the first hour (0-1h) and during first 2 hours (0-2h) after starting the infusion for minute ventilation (Figure 39A), end tidal
15 CO₂ (Figure 39B), respiratory rate (Figure 39C), and tidal volume (Figure 39D) in the second clinical study (GAL-021-102).

Figure 40 is a graph illustrating transcutaneous hemoglobin oxygen saturation (GAL-021-102).

Figure 41, comprising Figures 41A-C, illustrates results for Part I of
20 the GAL-021-104 clinical study: integrated percent change from baseline during the last ten minutes of each segment for minute ventilation (Figure 41A), tidal volume (Figure 41B) and respiratory rate (Figure 41C). Segments were thirty minutes in duration, except for the segment labeled (XXXVI)-high, which had duration of 40 minutes due to a twenty-minute loading dose infusion. The end-tidal was clamped
25 during the study and was largely invariant.

Figure 42 is a graph illustrating Part 2 of the GAL-021-104 study: Percent change in current at onset of the pain from a TENS device placed over anterior tibial area (n=8).

Figure 43, comprising Figures 43A-D, illustrates results for Part 2 of
30 the GAL-021-104 study: Integrated percent change from baseline during the last ten-minutes of each segment for minute ventilation (Figure 43A), end-tidal CO₂ (Figure 43B), respiratory rate (Figure 43C), and tidal volume (Figure 43D).

Figure 44, comprising Figures 44A-B, illustrate mean plasma concentration-time profiles of N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-

dimethyl-hydroxylamine hydrogen sulfate (XXXVI) following IV infusion to healthy volunteers during the First-in-Human study (Figure 44A) and the second study (Figure 44B).

5 DETAILED DESCRIPTION OF THE INVENTION

The present invention relates in one aspect to the unexpected discovery that the compounds of the invention are respiratory stimulants and useful in the treatment of breathing control disorders or diseases.

10 Definitions

As used herein, each of the following terms has the meaning associated with it in this section.

Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one skilled in the art to which this invention belongs. Generally, the nomenclature used herein and the laboratory procedures in animal pharmacology, pharmaceutical science, separation science and organic chemistry are those known and commonly employed in the art.

As used herein, the articles “a” and “an” refer to one or to more than one (i.e. to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

As used herein, the term “about” is understood by persons of ordinary skill in the art and varies to some extent on the context in which it is used. As used herein when referring to a measurable value such as an amount, a temporal duration, and the like, the term “about” is meant to encompass variations of $\pm 20\%$ or $\pm 10\%$, more preferably $\pm 5\%$, even more preferably $\pm 1\%$, and still more preferably $\pm 0.1\%$ from the specified value, as such variations are appropriate to perform the disclosed methods.

As used herein, a “subject” may be a human or non-human mammal. Non-human mammals include, for example, livestock and pets, such as ovine, bovine, porcine, canine, feline and murine mammals. Preferably, the subject is human.

In a non-limiting embodiment, the following terminology used to report blood gas measurements is well known to those skilled in the art and may be defined as such: minute ventilation (MV) is a measure of breathing volume per unit time and is given herein as mL/min; $p\text{CO}_2$ is partial pressure of carbon dioxide (gas)

in (arterial) blood measured in mm Hg (millimeters of Hg); pO_2 is partial pressure of oxygen (gas) in (arterial) blood measured in mmHg (millimeters of Hg); SaO_2 is the percentage of hemoglobin in the form of oxy-hemoglobin in blood; end-tidal CO_2 is the measurement of exhaled carbon dioxide gas as detected using colorimetry, or
5 capnometry.

As used herein, the term ED_{50} refers to the effective dose of a formulation that produces a given effect in 50 % of the subjects that are administered that formulation.

As used herein, a "disease" is a state of health of an animal wherein the
10 animal cannot maintain homeostasis, and wherein if the disease is not ameliorated then the animal's health continues to deteriorate.

As used herein, a "disorder" in an animal is a state of health in which the animal is able to maintain homeostasis, but in which the animal's state of health is less favorable than it would be in the absence of the disorder. Left untreated, a
15 disorder does not necessarily cause a further decrease in the animal's state of health.

As used herein, an "effective amount", "therapeutically effective amount" or "pharmaceutically effective amount" of a compound is that amount of compound that is sufficient to provide a beneficial effect to the subject to which the compound is administered. The term to "treat," as used herein, means reducing the
20 frequency with which symptoms are experienced by a patient or subject or administering an agent or compound to reduce the severity with which symptoms are experienced.

As used herein, the term "pharmaceutically acceptable" refers to a material, such as a carrier or diluent, which does not abrogate the biological activity
25 or properties of the compound useful within the invention, and is relatively non-toxic, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

As used herein, the term "salt" refers to an addition salt of free acid or
30 base that is useful within the methods of the invention. The term "salt" also refers to a mixture of a salt with its corresponding free acid or base, either in isolated form (e.g., as a solid) or in solution.

As used herein, the language "pharmaceutically acceptable salt" refers to a salt of the administered compound prepared from pharmaceutically acceptable

non-toxic acids and bases, including inorganic acids, inorganic bases, organic acids, inorganic bases, solvates, hydrates, and clathrates thereof.

As used herein, the term “composition” or “pharmaceutical composition” refers to a mixture of at least one compound useful within the invention
5 with a pharmaceutically acceptable carrier. The pharmaceutical composition facilitates administration of the compound to a subject.

As used herein, the term “pharmaceutically acceptable carrier” means a pharmaceutically acceptable material, composition or carrier, such as a liquid or solid filler, stabilizer, dispersing agent, suspending agent, diluent, excipient, thickening
10 agent, solvent or encapsulating material, involved in carrying or transporting a compound useful within the invention within or to the subject such that it may perform its intended function. Typically, such constructs are carried or transported from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other
15 ingredients of the formulation, including the compound useful within the invention, and not injurious to the subject. Some examples of materials that may serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate;
20 powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and
25 aluminum hydroxide; surface active agents; alginic acid; pyrogen-free water; isotonic saline; Ringer’s solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations. As used herein, “pharmaceutically acceptable carrier” also includes any and all coatings, antibacterial and antifungal agents, and absorption delaying agents, and the like that
30 are compatible with the activity of the compound useful within the invention, and are physiologically acceptable to the subject. Supplementary active compounds may also be incorporated into the compositions. The “pharmaceutically acceptable carrier” may further include a pharmaceutically acceptable salt of the compound useful within the invention. Other additional ingredients that may be included in the pharmaceutical

compositions used in the practice of the invention are known in the art and described, for example in Remington's Pharmaceutical Sciences (Genaro, Ed., Mack Publishing Co., 1985, Easton, PA), which is incorporated herein by reference.

As used herein, the phrase "process-related impurities" refers to
5 impurities formed during the process of making the active pharmaceutical ingredient, as caused by exposure of any starting material, intermediate, reactant, solvent, and the active pharmaceutical ingredient itself to the conditions of the synthetic process.

As used herein, "treating a disease or disorder" means reducing the frequency with which a symptom of the disease or disorder is experienced by a
10 subject. Disease and disorder are used interchangeably herein.

By the term "specifically bind" or "specifically binds," as used herein, is meant that a first molecule preferentially binds to a second molecule (*e.g.*, a particular receptor or enzyme), but does not necessarily bind only to that second molecule.

As used herein, the term "alkyl," by itself or as part of another
15 substituent means, unless otherwise stated, a straight or branched chain hydrocarbon having the number of carbon atoms designated (*i.e.* C₁-C₁₀ means one to ten carbon atoms) and includes straight, branched chain, or cyclic substituent groups. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl,
20 hexyl, and cyclopropylmethyl. Most preferred is (C₁-C₆)alkyl, such as, but not limited to, ethyl, methyl, isopropyl, isobutyl, *n*-pentyl, *n*-hexyl and cyclopropylmethyl.

As used herein, the term "cycloalkyl," by itself or as part of another substituent means, unless otherwise stated, a cyclic chain hydrocarbon having the
25 number of carbon atoms designated (*i.e.* C₃-C₆ means a cyclic group comprising a ring group consisting of three to six carbon atoms) and includes straight, branched chain or cyclic substituent groups. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Most preferred is (C₃-C₆)cycloalkyl, such as, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl
30 and cyclohexyl.

As used herein, the term "alkenyl," employed alone or in combination with other terms, means, unless otherwise stated, a stable mono-unsaturated or di-unsaturated straight chain or branched chain hydrocarbon group having the stated number of carbon atoms. Examples include vinyl, propenyl (or allyl), crotyl,

isopentenyl, butadienyl, 1,3-pentadienyl, 1,4-pentadienyl, and the higher homologs and isomers. A functional group representing an alkene is exemplified by $\text{-CH}_2\text{-CH=CH}_2$.

As used herein, the term “alkynyl,” employed alone or in combination
5 with other terms, means, unless otherwise stated, a stable straight chain or branched chain hydrocarbon group with a triple carbon-carbon bond, having the stated number of carbon atoms. Examples include ethynyl and propynyl, and the higher homologs and isomers.

As used herein, the term “substituted alkyl,” “substituted cycloalkyl,”
10 “substituted alkenyl” or “substituted alkynyl” means alkyl, cycloalkyl, alkenyl or alkynyl, as defined above, substituted by one, two or three substituents selected from the group consisting of halogen, -OH , alkoxy, tetrahydro-2-H-pyranyl, -NH_2 , $\text{-N(CH}_3)_2$, (1-methyl-imidazol-2-yl), pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, -C(=O)OH , trifluoromethyl, $\text{-C}\equiv\text{N}$, $\text{-C(=O)O(C}_1\text{-C}_4\text{)alkyl}$, -C(=O)NH_2 , $\text{-C(=O)NH(C}_1\text{-C}_4\text{)alkyl}$, $\text{-C(=O)N((C}_1\text{-C}_4\text{)alkyl)}_2$, $\text{-SO}_2\text{NH}_2$, -C(=NH)NH_2 , and -NO_2 , preferably
15 containing one or two substituents selected from halogen, -OH , alkoxy, -NH_2 , trifluoromethyl, $\text{-N(CH}_3)_2$, and -C(=O)OH , more preferably selected from halogen, alkoxy and -OH . Examples of substituted alkyls include, but are not limited to, 2,2-difluoropropyl, 2-carboxycyclopentyl and 3-chloropropyl.

As used herein, the term “alkoxy” employed alone or in combination
20 with other terms means, unless otherwise stated, an alkyl group having the designated number of carbon atoms, as defined above, connected to the rest of the molecule via an oxygen atom, such as, for example, methoxy, ethoxy, 1-propoxy, 2-propoxy (isopropoxy) and the higher homologs and isomers. Preferred are $(\text{C}_1\text{-C}_3)\text{alkoxy}$,
25 such as, but not limited to, ethoxy and methoxy.

As used herein, the term “halo” or “halogen” alone or as part of another substituent means, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom, preferably, fluorine, chlorine, or bromine, more preferably, fluorine or chlorine.

As used herein, the term “heteroalkyl” by itself or in combination with
30 another term means, unless otherwise stated, a stable straight or branched chain alkyl group consisting of the stated number of carbon atoms and one or two heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may be optionally oxidized and the nitrogen heteroatom may be optionally

quaternized. The heteroatom(s) may be placed at any position of the heteroalkyl group, including between the rest of the heteroalkyl group and the fragment to which it is attached, as well as attached to the most distal carbon atom in the heteroalkyl group. Examples include: -O-CH₂-CH₂-CH₃, -CH₂-CH₂-CH₂-OH, -CH₂-CH₂-NH-
5 CH₃, -CH₂-S-CH₂-CH₃, and -CH₂CH₂-S(=O)-CH₃. Up to two heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃, or -CH₂-CH₂-S-S-CH₃

As used herein, the term “heteroalkenyl” by itself or in combination with another term means, unless otherwise stated, a stable straight or branched chain monounsaturated or di-unsaturated hydrocarbon group consisting of the stated number
10 of carbon atoms and one or two heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. Up to two heteroatoms may be placed consecutively. Examples include -CH=CH-O-CH₃, -CH=CH-CH₂-OH, -CH₂-CH=N-OCH₃, -CH=CH-N(CH₃)-CH₃, and -CH₂-CH=CH-CH₂-SH.

15 As used herein, the term “aromatic” refers to a carbocycle or heterocycle with one or more polyunsaturated rings and having aromatic character, i.e. having (4n+2) delocalized π (pi) electrons, where n is an integer.

As used herein, the term “aryl,” employed alone or in combination with other terms, means, unless otherwise stated, a carbocyclic aromatic system
20 containing one or more rings (typically one, two or three rings) wherein such rings may be attached together in a pendent manner, such as a biphenyl, or may be fused, such as naphthalene. Examples include phenyl, anthracyl, and naphthyl. Preferred are phenyl and naphthyl, most preferred is phenyl.

As used herein, the term “aryl-(C₁-C₃)alkyl” means a functional group
25 wherein a one to three carbon alkylene chain is attached to an aryl group, *e.g.*, -CH₂CH₂-phenyl or -CH₂-phenyl (benzyl). Preferred is aryl-CH₂- and aryl-CH(CH₃)-. The term “substituted aryl-(C₁-C₃)alkyl” means an aryl-(C₁-C₃)alkyl functional group in which the aryl group is substituted. Preferred is substituted aryl(CH₂)-. Similarly, the term “heteroaryl-(C₁-C₃)alkyl” means a functional group
30 wherein a one to three carbon alkylene chain is attached to a heteroaryl group, *e.g.*, -CH₂CH₂-pyridyl. Preferred is heteroaryl-(CH₂)-. The term “substituted heteroaryl-(C₁-C₃)alkyl” means a heteroaryl-(C₁-C₃)alkyl functional group in which the heteroaryl group is substituted. Preferred is substituted heteroaryl-(CH₂)-.

As used herein, the term “heterocycle” or “heterocyclyl” or “heterocyclic” by itself or as part of another substituent means, unless otherwise stated, an unsubstituted or substituted, stable, mono- or multi-cyclic heterocyclic ring system that consists of carbon atoms and at least one heteroatom selected from the group consisting of N, O, and S, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen atom may be optionally quaternized. The heterocyclic system may be attached, unless otherwise stated, at any heteroatom or carbon atom that affords a stable structure. A heterocycle may be aromatic or non-aromatic in nature. In one embodiment, the heterocycle is a heteroaryl.

As used herein, the term “heteroaryl” or “heteroaromatic” refers to a heterocycle having aromatic character. A polycyclic heteroaryl may include one or more rings that are partially saturated. Examples include tetrahydroquinoline and 2,3-dihydrobenzofuryl.

Examples of non-aromatic heterocycles include monocyclic groups such as aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazoline, pyrazolidine, dioxolane, sulfolane, 2,3-dihydrofuran, 2,5-dihydrofuran, tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydropyridine, 1,4-dihydropyridine, piperazine, morpholine, thiomorpholine, pyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dioxane, 1,3-dioxane, homopiperazine, homopiperidine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin and hexamethyleneoxide.

Examples of heteroaryl groups include pyridyl, pyrazinyl, pyrimidinyl (such as, but not limited to, 2- and 4-pyrimidinyl), pyridazinyl, thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,3,4-thiadiazolyl and 1,3,4-oxadiazolyl.

Examples of polycyclic heterocycles include indolyl (such as, but not limited to, 3-, 4-, 5-, 6- and 7-indolyl), indolinyl, quinolyl, tetrahydroquinolyl, isoquinolyl (such as, but not limited to, 1- and 5-isoquinolyl), 1,2,3,4-tetrahydroisoquinolyl, cinnolinyl, quinoxalinyl (such as, but not limited to, 2- and 5-quinoxalinyl), quinazolinyl, phthalazinyl, 1,8-naphthyridinyl, 1,4-benzodioxanyl, coumarin, dihydrocoumarin, 1,5-naphthyridinyl, benzofuryl (such as, but not limited to, 3-, 4-, 5-, 6- and 7-benzofuryl), 2,3-dihydrobenzofuryl, 1,2-benzisoxazolyl, benzothienyl (such as, but not limited to, 3-, 4-, 5-, 6-, and 7-benzothienyl), benzoxazolyl, benzothiazolyl (such as, but not limited to,

2-benzothiazolyl and 5-benzothiazolyl), purinyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrrolizidinyl, and quinolizidinyl.

The aforementioned listing of heterocyclyl and heteroaryl moieties is intended to be representative and not limiting.

5 As used herein, the term “substituted” means that an atom or group of atoms has replaced hydrogen as the substituent attached to another group.

For aryl, aryl-(C₁-C₃)alkyl and heterocyclyl groups, the term “substituted” as applied to the rings of these groups refers to any level of substitution, namely mono-, di-, tri-, tetra-, or penta-substitution, where such substitution is permitted. The substituents are independently selected, and substitution may be at any chemically accessible position. In one embodiment, the substituents vary in number between one and four. In another embodiment, the substituents vary in number between one and three. In yet another embodiment, the substituents vary in number between one and two. In yet another embodiment, the substituents are independently selected from the group consisting of C₁₋₆ alkyl, -OH, C₁₋₆ alkoxy, halo, amino, acetamido and nitro. As used herein, where a substituent is an alkyl or alkoxy group, the carbon chain may be branched, straight or cyclic, with straight being preferred.

As used herein, the term “AcOH” refers to acetic acid; the term “nBuOH” refers to *n*-butanol; the term “CH₂Cl₂” refers to dichloromethane (also known as methylene dichloride); the term “DMSO” refers to dimethylsulfoxide; the term “EtOAc” refers to ethyl acetate; the term “EtOH” refers to ethanol; the term “HCl” refers to hydrochloric acid or a hydrochloride salt; the term “HPLC” refers to high pressure liquid chromatography; the term “H₂SO₄” refers to sulfuric acid; the term “LCMS” refers to liquid chromatography-mass spectrometry; the term “MS” refers to mass spectrometry; the term “MeOH” refers to methanol; the term “NaCl” refers to sodium chloride; the term “NaHCO₃” refers to sodium bicarbonate; the term “NaOH” refers to sodium hydroxide; the term “Na₂SO₄” refers to sodium sulfate; the term “mpk” refers to mg/kg; the term “NMR” refers to nuclear magnetic resonance; the term “PE” or “pet ether” refers to petroleum ether; the term “POCl₃” refers to phosphorous oxychloride; the term “ppm” refers to part per million; the term “xphos” refers to 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl; the term “dba” refers to *trans,trans*-dibenzylideneacetone.

“Instructional material,” as that term is used herein, includes a publication, a recording, a diagram, or any other medium of expression that can be used to communicate the usefulness of the composition and/or compound of the invention in a kit. The instructional material of the kit may, for example, be affixed to
5 a container that contains the compound and/or composition of the invention or be shipped together with a container that contains the compound and/or composition. Alternatively, the instructional material may be shipped separately from the container with the intention that the recipient uses the instructional material and the compound cooperatively. Delivery of the instructional material may be, for example, by physical
10 delivery of the publication or other medium of expression communicating the usefulness of the kit, or may alternatively be achieved by electronic transmission, for example by means of a computer, such as by electronic mail, or download from a website.

15 Compounds and Compositions of the Invention

The invention includes compounds of the invention, as well as any compositions comprising such compounds.

The invention includes at least one compound selected from the group consisting of: N-(2,4-bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine
20 (CLXXII), N-(2,4,6-tris-*n*-propylamino)-[1,3,5]triazine (CLXXIII), N-(2,4,6-tris-*n*-propylamino)-1,3-pyrimidine (CLXXIV), N-(2,4-bis-*n*-propylamino)-N-(6-*i*-propylamino)-1,3-pyrimidine (CLXXV), a salt thereof, and any combinations thereof.

In one embodiment, the salt is hydrogen sulfate, hydrochloride, phosphate, hydrogen phosphate or dihydrogen phosphate. In another embodiment,
25 the at least one compound is formulated with at least one pharmaceutically acceptable carrier.

The invention also includes a composition comprising N-(4,6-bis-*n*-propylamino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV) or a salt thereof, wherein 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol is present at a level equal
30 to or lower than about 1% (w/w) with respect to (XXXV) or the salt thereof.

In one embodiment, 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol is present at a level equal to or lower than about 0.5% (w/w) with respect to (XXXV) or the salt thereof. In another embodiment, 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol is present at a level equal to or lower than about 0.3% (w/w) with respect to (XXXV) or

the salt thereof. In yet another embodiment, 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol is present at a level equal to or lower than about 0.2% (w/w) with respect to (XXXV) or the salt thereof. In yet another embodiment, 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol is present at a level equal to or lower than about 0.15% (w/w) with respect to (XXXV) or the salt thereof. In yet another embodiment, 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol is present at a level equal to or lower than about 0.1% (w/w) with respect to (XXXV) or the salt thereof. In yet another embodiment, 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol is essentially absent from the composition.

The invention also includes a composition comprising N-(4,6-bis-*n*-propylamino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV) or a salt thereof, further comprising a buffer and a liquid carrier.

In one embodiment, the salt of (XXXV) is the hydrogen sulfate salt (XXXVI). In another embodiment, the composition further comprises citric acid. In yet another embodiment, the pH of the composition is adjusted with a base. In yet another embodiment, the base comprises sodium hydroxide. In yet another embodiment, the liquid carrier comprises water. In yet another embodiment, the pH of the composition ranges from about 2.5 to about 6. In yet another embodiment, the pH of the composition ranges from about 2.5 to about 5. In yet another embodiment, the pH of the composition ranges from about 3 to about 4. In yet another embodiment, the concentration of (XXXV) or the salt thereof in the composition is about 1-10 mg/mL. In yet another embodiment, the concentration of (XXXV) or the salt thereof in the composition is about 5-10 mg/mL. In yet another embodiment, the concentration of (XXXV) or the salt thereof in the composition is about 10 mg/mL. In yet another embodiment, the composition comprises less than about 0.5% (w/w) 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol (CLXXVIII) with respect to (XXXV). In yet another embodiment, less than about 0.5% (w/w) of N-(4,6-Bis-*n*-propylamino)-[1,3,5]-triazin-2-ol (CLXXVIII) with respect to (XXXV) forms over at least a 6-month period of storage of the composition at 2-8°C. In yet another embodiment, less than about 0.5% (w/w) of N-(4,6-Bis-*n*-propylamino)-[1,3,5]-triazin-2-ol (CLXXVIII) with respect to (XXXV) forms over at least a 12-month period of storage of the composition at 2-8°C. In yet another embodiment, less than about 0.5% (w/w) of N-(4,6-Bis-*n*-propylamino)-[1,3,5]-triazin-2-ol (CLXXVIII) with respect to (XXXV) forms over at least an 18-month period of storage of the composition at 2-8°C. In yet another embodiment, less than about 0.5% (w/w) of N-(4,6-Bis-*n*-propylamino)-

[1,3,5]-triazin-2-ol (CLXXVIII) with respect to (XXXV) forms over at least a 24-month period of storage of the composition at 2-8°C.

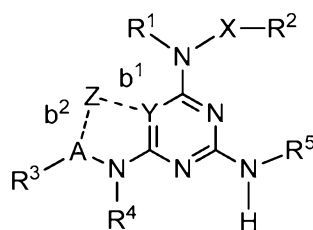
The invention also includes a crystalline free base of N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV), Form A,
5 with a XRPD spectrum as per Figure 22.

The invention also includes at least one crystalline salt of N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV) selected from the group consisting of: crystalline hydrogen sulfate salt (XXXVI) Form A, with a XRPD spectrum as per Figure 14; crystalline hydrogen sulfate salt (XXXVI)
10 comprising a mixture of Form A and Form B, with a XRPD spectrum as per Figure 23; crystalline hydrogen sulfate salt (XXXVI) Form C, with a XRPD spectrum as per Figure 24; crystalline hydrogen sulfate salt (XXXVI) Form D, with a XRPD spectrum as per Figure 25; crystalline hydrogen sulfate salt (XXXVI) comprising a mixture of Form A and Form D, with a XRPD spectrum as per Figure 26; crystalline phosphoric
15 acid salt (CLXXX) Form A, with a XRPD spectrum as per Figure 27; crystalline phosphoric acid salt (CLXXX) Form C, with a XRPD spectrum as per Figure 28; crystalline phosphoric acid salt (CLXXX) comprising a mixture of Form A and Form B, with a XRPD spectrum as per Figure 29; crystalline phosphoric acid salt (CLXXX) comprising a mixture of Form C and Form D, with a XRPD spectrum as per Figure
20 30; crystalline phosphoric acid salt (CLXXX) comprising a mixture of Form C and Form E, with a XRPD spectrum as per Figure 31; and any mixtures thereof.

The invention also includes a salt of N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine (XXXV), comprising approximately one mole equivalent of sulfuric acid. In one embodiment, the salt further comprises one mole
25 equivalent of water.

The invention also includes a salt of N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV), comprising at least one mole equivalent of phosphoric acid. In one embodiment, the salt comprises about one mole equivalent of phosphoric acid.

30 The invention also includes a compound of formula (I) or a salt thereof:



(I), wherein

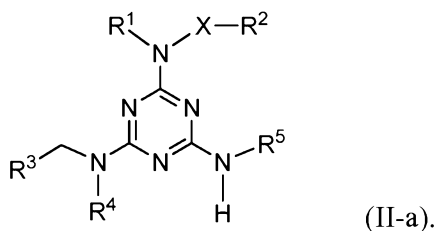
- R^1 and R^2 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl; or R^1 and R^2 combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl; R^3 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-NR^1R^2$, $-C(O)OR^1$, acyl, or aryl; R^4 is H, alkyl, or substituted alkyl; R^5 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-OR^1$, $-NR^1R^2$, $-C(O)OR^1$, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, or substituted heterocyclic; or R^3 and R^5 combine as to form a biradical selected from the group consisting of 3,6,9-trioxa-undecane-1,11-diyl and 3,6-dioxa-octane-1,8-diyl; R^6 is H, alkyl, substituted alkyl or alkenyl; X is a bond, O or NR^4 ; and, Y is N, CR^6 or C; wherein:

if Y is N or CR^6 , then bond b^1 is nil and: (i) Z is H, bond b^2 is a single bond, and A is CH; or, (ii) Z is nil, bond b^2 is nil, and A is a single bond; and,

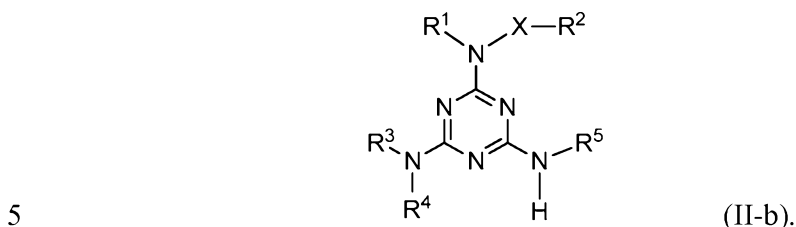
- if Y is C, then bond b^1 is a single bond, and: (i) Z is CH_2 , bond b^2 is a single bond, and A is CH; or, (ii) Z is CH, bond b^2 is a double bond, and A is C.

In one embodiment, R^3 is H, alkyl, substituted alkyl, alkenyl, cycloalkyl, substituted cycloalkyl, or substituted alkenyl. In another embodiment, R^5 is H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, acyl, cycloalkyl or substituted cycloalkyl.

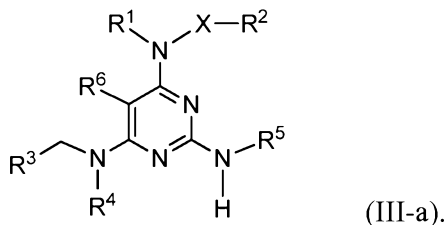
- In one embodiment, Y is N, bond b^1 is nil, Z is H, bond b^2 is a single bond, A is CH, and the compound of the invention is a 1,3,5-triazine of formula (II-a) or a salt thereof:



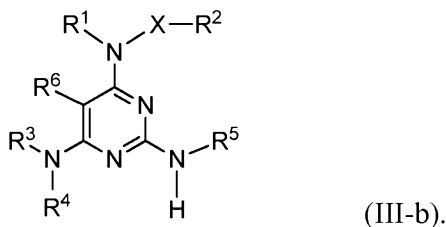
In one embodiment, Y is N, bond b¹ is nil, Z is nil, bond b² is nil, and A is a bond, and the compound of the invention is a 1,3,5-triazine of formula (II-b) or a salt thereof:



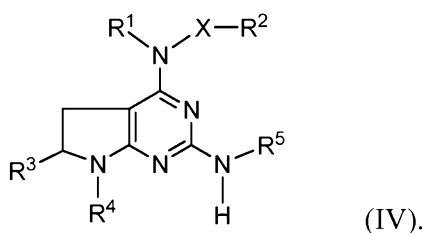
In one embodiment, Y is CR⁶, bond b¹ is nil, Z is H, bond b² is a single bond, A is CH, and the compound of the invention is a pyrimidine of formula (III-a) or a salt thereof:



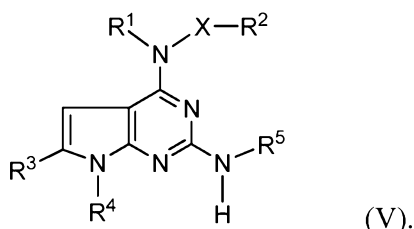
In one embodiment, Y is CR⁶, bond b¹ is nil, Z is nil, bond b² is nil, and A is a bond, and the compound of the invention is a pyrimidine of formula (III-b) or a salt thereof:



In one embodiment, Y is C, bond b¹ is a single bond, Z is CH₂, bond b² is a single bond, A is CH, and the compound of the invention is a pyrrolidinopyrimidine of formula (IV) or a salt thereof:



In one embodiment, Y is C, bond b¹ is a single bond, Z is CH, bond b² is a double bond, A is C, and the compound of the invention is a pyrrolopyrimidine of formula (V) or a salt thereof:



In one embodiment, the compound of formula (I) is selected from the group consisting of: N-(4,6-Bis-methylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-ethylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-Cyclopropylmethyl)-N-(6-*n*-propylamino) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-Ethylamino)-N-(6-*n*-propylamino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2-methylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2,2-dimethylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2,2-dimethylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-(Methoxy(methyl)amino)-6-(*n*-propylamino)-1,3,5-triazin-2-yl)propionamide, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-methyl-hydroxylamine, O-Allyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine, 6-(Methoxy(methyl)amino)-N²-propyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine, O-Benzyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-isopropyl-hydroxylamine, 6-[1,2]Oxazinan-2-yl-N,N'-dipropyl-[1,3,5]triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-N-methyl-hydroxylamine, O-Benzyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-hydroxylamine, 6-

((Benzyloxy)(isopropyl) amino)-N²,N⁴-dipropyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-O-isopropyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isobutyl-N-methyl-hydroxylamine, 6-(Methyl(thiophen-2-ylmethoxy)amino)-N²,N⁴-dipropyl-1,3,5-triazine-2,4-diamine, N-
 5 (4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-cyclopropylmethyl-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-ethyl-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-(2,2-difluoro-ethyl)-hydroxylamine, 4-N-(2-Dimethylaminoethyl)amino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4-N-(3-(1-N-Methylimidazol-2-yl)-propyl)-amino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4-N-(1-N-Methylimidazol-2-yl)-methylamino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-(N-(2-dimethylaminoethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-(N-(pyridin-4-yl-methyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-
 15 hydroxylamine, 4,6-Bis-[N-(3-methoxy-*n*-propyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-[N-(tetrahydropyran-4-yl-methyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(5,8,11-Trioxa-2,14,16,18,19-pentaazabicyclo[13.3.1]nonadeca-1(18),15(19),16(17)-trien-17-yl)-N,O-dimethylhydroxylamine, 2,6-Bis-(N-*n*-propylamino)-[1,3]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N',N'-dimethylhydrazine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-N'-methylhydrazine, 2-(*n*-Propyl)amino-4-(*i*-propylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine, 2-(*n*-Propyl)amino-4-dimethylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine, 2-(*n*-Propyl)amino-4-methylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine, 2-(*n*-Propyl)amino-4-(*i*-propyl)amino-7-*i*-propyl-pyrrolidino[2,3-d]pyrimidine, 2,4-Bis-(*n*-propyl)amino-7H-pyrrolidino[2,3-d]pyrimidine, 2-(*n*-Propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-methyl-pyrrolidino[2,3-d]pyrimidine, 8-(7-Methyl-2-(*n*-propylamino)-pyrrolidino[2,3-d]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol, N-(2-Propylamino-7H-pyrrolo[2,3d]pyrimidin-4-yl)-
 30 N,O-dimethyl-hydroxylamine, N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-

hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine, N-Methyl-N-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine, N,N-Dimethyl-N'-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine, N-(2,4-Bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine, N-(2,4,6-Tris-*n*-propylamino)-[1,3,5]triazine, N-(2,4,6-Tris-*n*-propylamino)-1,3-pyrimidine, N-(2,4-Bis-*n*-propylamino)-N-(6-*i*-propylamino)-1,3-pyrimidine, a salt thereof and mixtures thereof.

In one embodiment, the at least one compound is 2,6-bis-(N-*n*-propylamino)-[1,3]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine or a salt thereof. In another embodiment, the salt is hydrogen sulfate, hydrochloride, phosphate, hydrogen phosphate or dihydrogen phosphate.

In one embodiment, the at least one compound is selected from the group consisting of: 2-(*n*-Propyl)amino-4-(*i*-propylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine (CXXVI), 2-(*n*-Propyl)amino-4-dimethylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine (CXXVIII), 2-(*n*-Propyl)amino-4-methylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine (CXXXI), 2-(*n*-Propyl)amino-4-(*i*-propyl)amino-7-*i*-propyl-pyrrolidino[2,3-d]pyrimidine (CXXXVI), 2,4-Bis-(*n*-propyl)amino-7H-pyrrolidino[2,3-d]pyrimidine (CXLIX), 2-(*n*-Propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-methyl-pyrrolidino[2,3-d]pyrimidine (CLII), 8-(7-Methyl-2-(propylamino)-pyrrolidino[2,3-d]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol (CLV), a salt thereof and mixtures thereof. In another embodiment, the salt is hydrogen sulfate, hydrochloride, phosphate, hydrogen phosphate or dihydrogen phosphate.

In one embodiment, the at least one compound is selected from the group consisting of: N-(2-Propylamino-7H-pyrrolo[2,3d]pyrimidin-4-yl)-O,N-dimethyl-hydroxylamine (CXLI), N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine (CLVIII), N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine (CLX), N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O,N-dimethyl-hydroxylamine (CLXII), N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine (CLXIV), N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine (CLXVI), N-Methyl-N-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine (CLXVIII), N,N-dimethyl-N'-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine (CLXX), a salt thereof

and mixtures thereof. In another embodiment, the salt is hydrogen sulfate, hydrochloride, phosphate, hydrogen phosphate or dihydrogen phosphate.

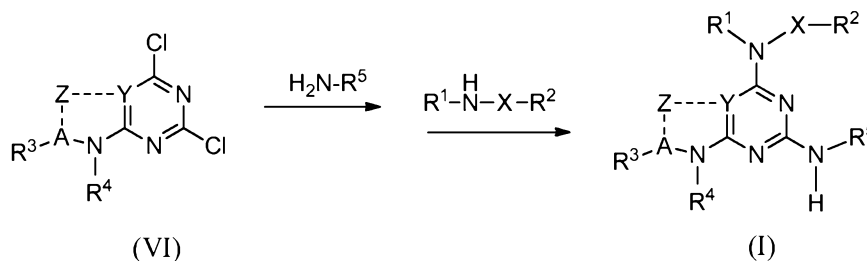
In one embodiment, the compound is formulated with at least one pharmaceutically acceptable carrier.

5

Preparation of the Compounds of the Invention

The compounds of the invention may be prepared according to the general methodology illustrated in the synthetic schemes described below. The reagents and conditions described herein may be modified to allow the preparation of the compounds of the invention, and such modifications are known to those skilled in the art. The scheme included herein are intended to illustrate but not limit the chemistry and methodologies that one skilled in the art may use to make compounds of the invention.

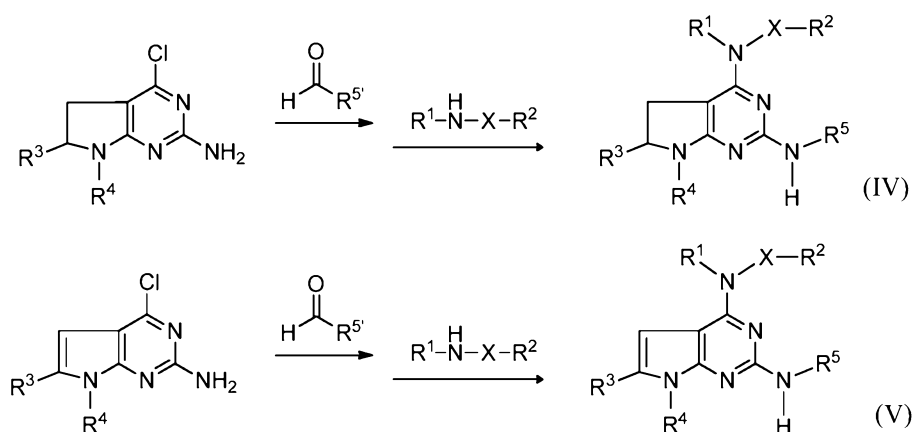
In one aspect, compounds of formula (I) may be prepared by the successive additions of (i) primary amines, (ii) a N-alkoxy-N-alkylamine or (iii) an appropriately substituted hydrazine ($\text{H}_2\text{N-NHR}^2$ or $\text{R}^1\text{HN-NHR}^2$) to suitably chlorinated intermediate (VI), as illustrated below in Scheme 1.



Scheme 1

20

In another aspect, a compound of formula (IV) or (V) may be prepared by reductive alkylation of a suitably chlorinated amino-pyrrolidino-pyrimidine or amino-pyrrolo-pyrimidine, respectively (Scheme 2).



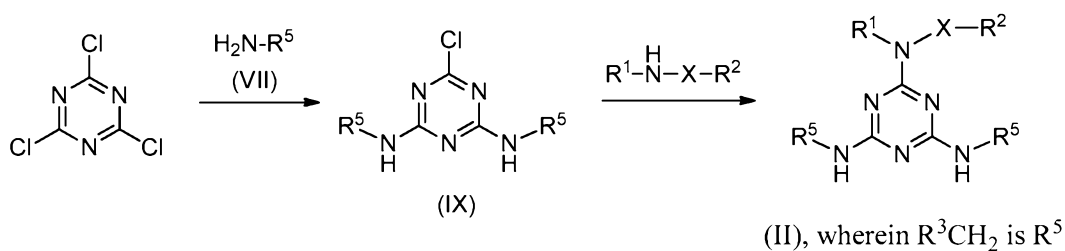
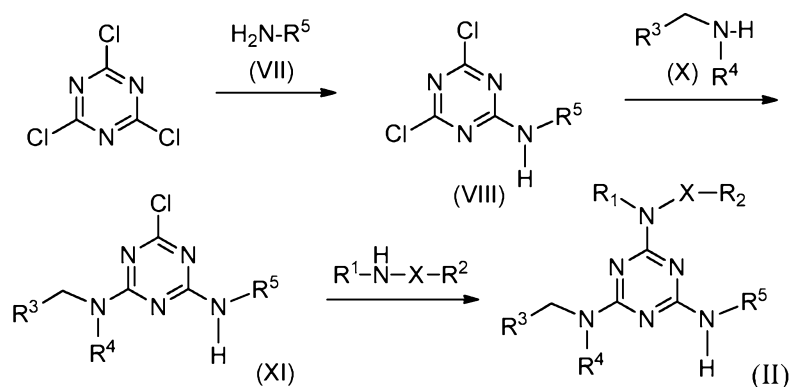
Scheme 2

In yet another aspect, a triazine compound of formula (II) may be prepared by the successive additions of primary amines and (i) a N-alkoxy-N-alkylamine, (ii) a hydrazine $\text{H}_2\text{N-NHR}^2$, or (iii) a hydrazine $\text{R}^1\text{HN-NHR}^2$ to a suitably chlorinated triazine. Under appropriate conditions, the reaction may allow the addition of either one or two amine substituents to the triazine ring. Alternatively, first the N-alkoxy-N-alkylamine, the hydrazine $\text{H}_2\text{N-NHR}^2$, or the hydrazine $\text{R}^1\text{HN-NHR}^2$ may be added to the triazine, followed by the addition of the amines.

In a non-limiting example, to a solution of 2,4,6-trichlorotriazine in an appropriate aprotic or protic solvent containing an inorganic or organic base, is added a solution of a primary amine (VII) and the reaction is allowed to proceed at ambient temperature or heated, to isolate mono-amine adduct (VIII) or bis-amine adduct (IX).

In a subsequent reaction, mono-amine adduct (VIII) is reacted with another primary amine or a secondary amine (X) to yield the unsymmetrical monochloro-bis-amino-triazine adduct (XI). In a subsequent reaction, monochloro-bis-amino-triazine adduct (XI) is reacted with (i) a N-alkoxy-N-alkylamine, (ii) a hydrazine $\text{H}_2\text{N-NHR}^2$ or (iii) a hydrazine $\text{R}^1\text{HN-NHR}^2$ in an appropriate aprotic or protic solvent containing an inorganic or organic base to produce desired compounds of formula (II) (Scheme 3).

Alternatively, in a subsequent reaction, bis-amine adduct (IX) is reacted with (i) a N-alkoxy-N-alkylamine, (ii) a hydrazine $\text{H}_2\text{N-NHR}^2$ or (iii) a hydrazine $\text{R}^1\text{HN-NHR}^2$ in an appropriate aprotic or protic solvent containing an inorganic or organic base to produce desired compounds of formula (II), wherein R^3CH_2 is R^5 (Scheme 4).

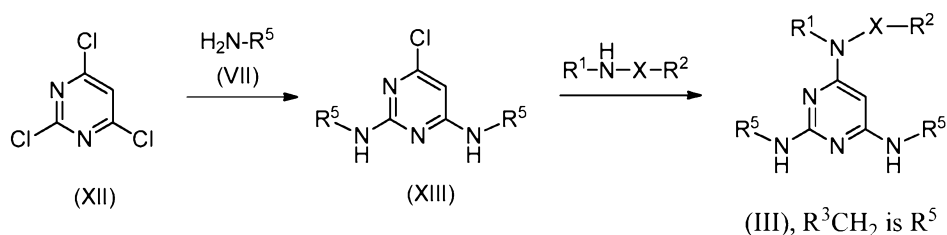


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Scheme 4

In yet another aspect, the pyrimidine compound of the formula (III) may be prepared by the successive additions of primary amines and (i) a N-alkoxy-N-alkylamine, (ii) a hydrazine H_2N-NHR^2 or (iii) a hydrazine $R^1HN-NHR^2$ to a suitably chlorinated pyrimidine.

In a non-limiting example, to a solution of 2,4,6-trichloropyrimidine (XII) in an appropriate aprotic or protic solvent containing an inorganic or organic base is added a solution of a primary amine (VII) and the reaction is allowed to proceed at ambient temperature or heated, yielding bis-amine adduct (XIII). In a subsequent reaction, bis-amine adduct (XIII) is reacted with (i) a N-alkoxy-N-alkylamine, (ii) a hydrazine H_2N-NHR^2 , or (iii) a hydrazine $R^1HN-NHR^2$ in an appropriate aprotic or protic solvent containing an inorganic or organic base to produce desired compounds of formula (III) (Scheme 5).



Scheme 5

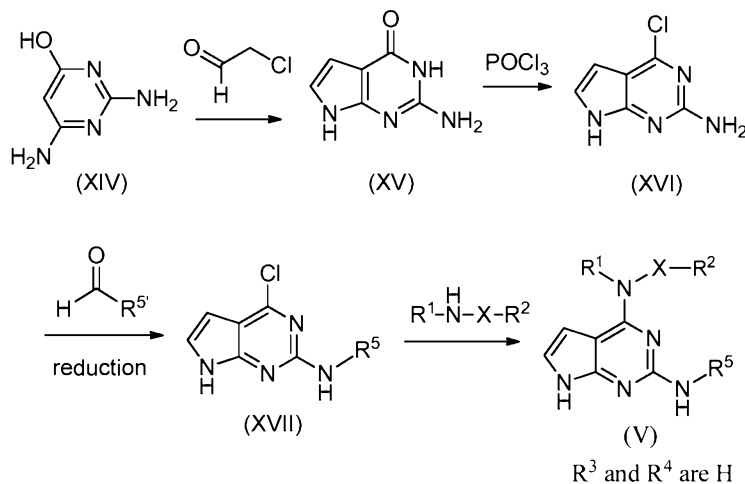
In yet another aspect, a pyrrolidino-pyrimidine of formula (IV) or a
 5 pyrrolo-pyrimidine compounds of formula (V) may be prepared from an appropriately
 chlorinated aminopyrrolidinopyrimidine or aminopyrrolopyrimidine intermediate,
 respectively.

In a non-limiting example, 2-chloroacetaldehyde may be added to a
 solution of 2,6-diamino-4-hydroxy-1,3-pyrimidine (XIV) in a polar protic solvent, at
 10 ambient temperature or under heating, to yield cyclized adduct (XV). Subsequent
 treatment with a chlorinating agent, such as, but not limited to, phosphorous
 oxychloride produces the chloro intermediate (XVI). Intermediate (XVI) may be
 submitted to reductive alkylation with an aldehyde in the presence of a reducing
 agent, such as a borohydride (in a non-limiting example, cyanoborohydride) in a
 15 protic solvent, at ambient temperature or elevated temperature, to produce the amino
 substituted adduct (XVII). In a subsequent reaction, amino substituted adduct (XVII)
 is reacted with (i) a N-alkoxy-N-alkylamine, (ii) a hydrazine $\text{H}_2\text{N-NHR}^2$, or (iii) a
 hydrazine $\text{R}^1\text{HN-NHR}^2$ in an appropriate aprotic or protic solvent containing an
 inorganic or organic base to produce desired compounds of formula (V), wherein R^3
 20 and R^4 are H (Scheme 6).

In a non-limiting example, a pyrrolidinopyrimidine compound of the
 formula (IV) may be prepared from the corresponding pyrrolopyrimidine analog via
 reduction (Scheme 7).

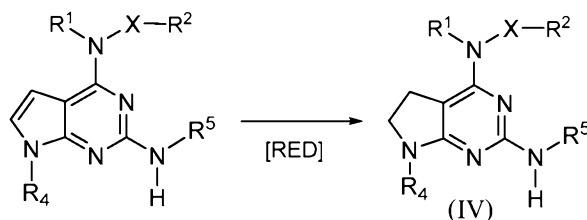
The manufacture of active pharmaceutical ingredients (APIs) may
 25 introduce or generate impurities in an intermediate or final active pharmaceutical
 compound. These impurities may include trace metals, processing aide residuals
 (e.g., silica, cellulose fibers), or solvents derived from purchased starting materials.
 Other impurities may form as a consequence of the conditions to which the starting
 materials, process intermediates, or active ingredient itself are exposed. These
 30 impurities may be problematic, affecting the manufacturing process as a whole and

the active ingredient in particular (*e.g.*, its purity and crystallinity, and conditions for its isolation or crystallization). Such impurities often carry forward into the isolated API.



5

Scheme 6



Scheme 7

10 Process-related impurities derived from degradation or side reactions involving the starting materials, intermediates, reactants, solvents or APIs are often related to the structure of the API itself. Regulatory guidances (*e.g.*, IQC Q3b R3) provide accepted limits to which such potentially structurally related species may be present in the active ingredient, and provide threshold levels above which such

15 impurities should be identified, or both identified and qualified with toxicology data. In some instances, a given impurity may be present within acceptable levels and still affect the behavior of the active ingredient as a drug product formulated for exploratory or approved medical use. For example, a process impurity present within acceptable levels in the active ingredient from a regulatory perspective may form an

20 unacceptable precipitate in preparations for parenteral use.

Under certain conditions where the compounds of the present invention and their synthetic intermediates are exposed to acidic or alkaline aqueous environments, the bond between the aromatic heterocycle and the ring substituents may be susceptible to hydrolytic cleavage. For example, in the intermediates to compounds of formula (II-a), a halo substituent in the 2 position (Schemes 3 and 4) may be hydrolytically replaced with a hydroxyl group to yield N-(4,6-Bis(*n*-propylamino)-1,3,5-triazin-2-ol (CLXXVIII). Similarly, the amine substituents of compounds of formula (II-a) may be displaced by a hydroxyl group. Without wishing to be bound by theory, a series of chemical changes may occur to enable this substitution, such as a prior oxidation of the appended amine side chain, with hydrolytic replacement by hydroxyl as the final transformation. As a specific non-limiting example, the N,O-dimethylhydroxylamino substituent of N-(4,6-Bis(*n*-propylamino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV) may be partially displaced by hydroxyl during processing in the presence of water, forming (CLXXVIII) as a process impurity. (CLXXVIII) is unreported, has very low solubility in most organic solvents and is sparingly soluble in aqueous environments. It was unexpectedly observed that even at elevated temperatures (CLXXVIII) is very insoluble relative to the active ingredient. Thus, trace quantities of this compound in the API can be problematic in liquid formulations. In one embodiment, (CLXXVIII) formed during processing is removed from the system by filtering a solution of the active ingredient as the free base at an elevated temperature. Remaining levels of the impurity present after such filtration may be purged during solid product isolation in the mother liquor and final product washes. In one embodiment, the level of (CLXXVIII) in the isolated (XXXVI) is less than 1% (w/w) with respect to (XXXVI). In yet another embodiment, the level of (CLXXVIII) in the isolated (XXXVI) is less than 0.5% (w/w) with respect to (XXXVI). In yet another embodiment, the level of (CLXXVIII) in the isolated (XXXVI) is less than 0.3% (w/w) with respect to (XXXVI). In yet another embodiment, the level of (CLXXVIII) in the isolated (XXXVI) is less than 0.2% (w/w) with respect to (XXXVI). In yet another embodiment, the level of (CLXXVIII) in the isolated (XXXVI) is less than 0.15% (w/w) with respect to (XXXVI). In yet another embodiment, the level of (CLXXVIII) in the isolated (XXXVI) is less than 0.1% (w/w) with respect to (XXXVI). In yet another embodiment, the isolated (XXXVI) is essentially free of 4,6-bis(*n*-propylamino)-1,3,5-triazin-2-ol (CLXXVIII).

Formulation and Drug Product Stability

Extensive experimentation was conducted to devise a suitable liquid formulation for (XXXVI). Experimentation had shown the pKa of (XXXVI) to be ca.

5 5.6. A pH solubility study was performed to assess the feasibility of formulating (XXXVI) as a simple buffer solution at a reasonable pH for an IV formulation. Solubility was assessed for (XXXV) alone (Figure 19A) or when admixed with citric acid and adjusted to pH 3-5.5 with 6N sodium hydroxide (Figure 19B). From the resulting data (Table 12A, Figure 19B), solubility of (XXXV) was calculated to be 10
10 mg/mL at ca. pH 3.86, 25 mg/mL at ca. pH 3.46, and 50 mg/mL at ca. pH 3.16. The solubility studies in water suggested solubility might be inadequate above a pH of ca. 3.6 to enable useful concentrations. Formulation at pH <3.6 may be tolerable when the formulated drug is diluted prior to administration, however the drug stability could be an issue at such a low pH.

15 To further evaluate the possibility for an all-aqueous formulation, stability studies of (XXXV) as a function of pH were undertaken in the presence of a buffer, with special attention to drug and buffer concentration to minimize drug precipitation and avoid buffer-catalyzed drug degradation (Figure 20A, Table 12B). (XXXVI) in water (1 mg/mL) was admixed with a solution of citric acid and glycine
20 (10 mM each), the mix adjusted to pH 2-5, and exposed to 40°C, 60°C, 25°C (control) and -70°C (control) and evaluated for physical appearance, pH, assay and related substances after 1 week, 2 weeks and 4 weeks of storage. At 40°C and 60°C, degradant levels at pH 2 were ca. 10-fold higher vs. pH 3-6, however at pH 3-6 growth in impurities to levels > 0.2 was generally still observed. Due to the limited solubility
25 of (XXXV) above pH 3.6, the stability was evaluated in the pH range 2-3.6 using methodology similar to that used for pH 2-5 (Figure 20B, Table 12C). Assay and sample pH showed little change, however impurities growth occurred across the range, with impurity levels at pH 2 $\geq$ 10 fold higher than impurity levels at pH 3.6.

As another option, formulations including a co-solvent matrix could be
30 useful in providing good solubility for the salt and free base forms at a suitable pH. The solubilities of (XXXV) and (XXXVI) were evaluated in various solvents and standard IV solutions, including 0.9% NaCl, 5% dextrose, ethanol, methanol, acetonitrile, 30% PEG 400, 70% PEG 400 and 100% PEG 400, 5% Tween 80, and propylene glycol (Table 12D). The solubility of (XXXVI) exceeded 90 mg/mL in

water (>400 mg/mL), IV solutions (0.9% saline and 5% dextrose), ethanol and methanol, and in 30%, 70% and 100% propylene glycol. Its solubility in 100% PEG-400 was ca. 36mg/mL but ≥ 90 mg/mL in 30 % and 70% PEG-400. The saturation solubility of (XXXV) in water was ca. 0.21 mg/mL, which agreed with the predicted value from the pH solubility study. The solubility in ethanol, methanol and acetonitrile were > 90 mg/mL. The solubility in PEG-400 and propylene glycol systems improved with increasing levels of the cosolvent.

The impact of buffer strength on stability was studied using admixtures of (XXXV) with 10-250 mmole citric acid at pH 3 (Table 12F). Impurity levels increased noticeably at the highest buffer concentration, but there was no effect of buffer strength at 40 °C within the range of buffer concentration relevant to the formulation (ca. 10-50 mM).

A total of nine (XXXVI) formulation prototypes were prepared, including a simple buffered solution, co-solvent systems as well as non-aqueous solutions (Table 12G). The solutions were prepared at 25 mg/mL (XXXV) as free base, corresponding to 35 mg/mL (XXXVI). Prototypes 6, 7 and 8 resulted in significant precipitation during preparation and hence were not evaluated further. The remaining prototypes were stored at 2-8°C, room temperature, 40°C and 60°C in serum vials. Samples stored at 2-8°C and RT were analyzed at selected time points for stability (Tables 12G.1-12G.6).

The study suggested that a buffered aqueous formulation of (XXXV) near pH 3 would be stable under refrigerated or 25°C conditions (Table 12G.1). Based on the data used to prepare Figure 19B, reducing the (XXXV) concentration by half would allow the formulation pH to be increased by about 0.3 units, and as can be seen in Table 12C, a 0.3 unit pH increase substantially improved stability of the formulation. Accordingly, the concentration of (XXXV) in the formulation as per Table 12G, line 1, was reduced from 25 mg/mL to 10 mg/mL, the pH increased from 3.0 to 3.2, and the buffer concentration was proportionately decreased from 50 mM to 20 mM. The final formulation is provided in Table 12H.

A batch of (XXXVI) formulated for clinical use was placed under formal GMP stability (Tables 20I.1 and 12I.2). The data obtained indicate that a single degradant was formed over time. The degradant was identified as N-(4,6-Bis(propylamino)-1,3,5-triazin-2-ol (CLXXVIII). The result of the GMP stability

study indicated the degradant can be expected to remain below 0.5% for at least two years (Figure 21, Table 12J).

In one aspect, when compounds of the invention are partly or entirely dissolved in water or aqueous mixtures comprising suitable organic solvents, hydrolytic degradants may be observed over time. For example, N-(4,6-Bis-n-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV) may degrade to 4,6-Bis(propylamino)-1,3,5-triazin-2-ol (CLXXVIII) in water-based formulations. Degradation was increasingly more pronounced as the pH was reduced below a value of 3 (Figures 20A and 20B). For (XXXV) solubility was high at pH 3.5 or lower, and decreased rapidly at ca. pH 3.5 to ca. 4.4 (Figures 19A and 19B).

In another aspect, the pH of the mixture containing (XXXV) is adjusted to a specific range to balance solubility and hydrolytic stability at any temperature selected. The rate of degradation for (XXXV) was highest in the pH range where (XXXV) is soluble to clinically useful levels. In one embodiment, the clinically useful concentration of (XXXV) in a liquid carrier is about 1-10 mg/mL. In another embodiment, the clinically useful concentration of (XXXV) in a liquid carrier is about 5-10 mg/mL. Degradation of (XXXV) in an aqueous environment was also highly temperature-dependent, wherein cold temperatures slowed degradation.

In one embodiment, (XXXV) as its hydrogen sulfate salt (XXXVI) in a liquid carrier is admixed with agents to adjust pH to optimize solubility and minimize degradation. In another embodiment, (XXXV) as its hydrogen sulfate salt (XXXVI) in a liquid carrier is admixed with a buffering aid. Suitable buffering aids include, but are not limited to citric acid, ascorbic acid, monobasic phosphoric acid, and lactic acid. In an embodiment, the buffering aid is citric acid. In another embodiment, (XXXV) as its hydrogen sulfate salt (XXXVI) is admixed with citric acid and a base to adjust pH as necessary to optimize solubility and minimize hydrolytic degradation. Suitable bases include, but are not limited to, sodium hydroxide, potassium hydroxide, ammonium hydroxide, and dibasic potassium hydrogen phosphate. In one embodiment, the pH is adjusted with sodium hydroxide. In another embodiment, the liquid carrier is a mixture of water and a suitable organic co-solvent. Suitable organic co-solvents include, but are not limited to, glycerin, propylene glycol, polyethylene glycol 400, ethanol, 1,4-butanediol, and dimethylsulfoxide. In another embodiment, the liquid carrier is water.

In one embodiment, the mixture comprising (XXXV) as its sulfate salt (XXXVI) with citric acid and sodium hydroxide in water is adjusted to a pH of about 2.5 to 6. In another embodiment, the mixture is adjusted to a pH of about 3 to 5. In yet another embodiment, the mixture is adjusted to a pH of about 3 to 4.

5 In one embodiment, the mixture comprising (XXXV) as its hydrogen sulfate salt may be stored at low temperatures to retard the rate of degradation of the compound. In another embodiment, the temperature may be in the range of about 0-15°C. In yet another embodiment, the cold temperature may be in the range of 2-8°C. In yet another embodiment, the mixture comprising (XXXV) as its hydrogen sulfate
10 salt (XXXVI) and citric acid and sodium hydroxide is adjusted to pH of about 3-4 and stored at about 2-8 °C. The rate of degradant growth was slow at 2-8°C and much faster at 25°C or above. As illustrated in Figure 21, the level of (CLXXVIII) formed when (XXXVI) is formulated for parenteral administration (non-limiting conditions: aqueous media at pH 3-4) may be maintained below 0.5% for over 2 years by storing
15 the preparation at 2-8°C (Figure 21).

The present invention includes a formulation comprising an active ingredient, salt former, admixed buffering aid, admixed base pH and liquid carrier, along with storage conditions necessary to optimize drug solubility and maintain hydrolytic degradants within acceptable levels.

20

Salts

The compounds described herein may form salts with acids, and such salts are included in the present invention. In one embodiment, the salts are pharmaceutically acceptable salts. The term “salts” embraces addition salts of free
25 acids that are useful within the methods of the invention. The term “pharmaceutically acceptable salt” refers to salts that possess toxicity profiles within a range that affords utility in pharmaceutical applications. Pharmaceutically unacceptable salts may nonetheless possess properties such as high crystallinity, which have utility in the practice of the present invention, such as for example utility in process of synthesis, purification or formulation of compounds useful within the methods of the invention.
30

Suitable pharmaceutically acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of inorganic acids include sulfate, hydrogen sulfate, hydrochloric, hydrobromic, hydriodic, nitric, carbonic, sulfuric, and phosphoric acids (including hydrogen phosphate and

dihydrogen phosphate). Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, trifluoromethanesulfonic, 2-hydroxyethanesulfonic, p-toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, alginic, β -hydroxybutyric, salicylic, galactaric and galacturonic acid.

Suitable pharmaceutically acceptable base addition salts of compounds of the invention include, for example, metallic salts including alkali metal, alkaline earth metal and transition metal salts such as, for example, calcium, magnesium, potassium, sodium and zinc salts. Pharmaceutically acceptable base addition salts also include organic salts made from basic amines such as, for example, N,N'-dibenzylethylene-diamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared from the corresponding compound by reacting, for example, the appropriate acid or base with the compound.

Combination Therapies

In one embodiment, the compounds of the invention are useful in the methods of present invention in combination with at least one additional compound useful for treating breathing control disorders. These additional compounds may comprise compounds of the present invention or other compounds, such as commercially available compounds, known to treat, prevent, or reduce the symptoms of breathing disorders. In embodiment, the combination of at least one compound of the invention or a salt thereof and at least one additional compound useful for treating breathing disorders has additive, complementary or synergistic effects in the treatment of disordered breathing, and in the treatment of sleep-related breathing disorders.

In a non-limiting example, the compounds of the invention or a salt thereof may be used in combination with one or more of the following drugs: acetazolamide, almitrine, theophylline, caffeine, methylprogesterone and related compounds, serotonergic modulators, cannabinoids (such as but not limited to dronabinol), and compounds known as ampakines. Non-limiting examples of

ampakines are the pyrrolidine derivative racetam drugs such as piracetam and aniracetam; the "CX" series of drugs which encompass a range of benzoylpiperidine and benzoylpyrrolidine structures, such as CX-516 (6-(piperidin-1-yl-carbonyl)quinoxaline), CX-546 (2,3-dihydro-1,4-benzodioxin-7-yl-(1-piperidyl)-methanone), CX-614 (2H,3H,6aH-pyrrolidino(2,1-3',2')-1,3-oxazino-(6',5'-5,4)benzo(e)1,4-dioxan-10-one), CX-691 (2,1,3-benzoxadiazol-6-yl-piperidin-1-yl-methanone), CX-717, CX-701, CX-1739, CX-1763, and CX-1837; benzothiazide derivatives such as cyclothiazide and IDRA-21 (7-chloro-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide); biarylpropylsulfonamides such as LY-392,098, LY-404,187 (N-[2-(4'-cyanobiphenyl-4-yl)propyl]propane-2-sulfonamide), LY-451,646 and LY-503,430 (4'-{(1S)-1-fluoro-2-[(isopropylsulfonyl)amino]-1-methylethyl}-N-methylbiphenyl-4-carboxamide).

A synergistic effect may be calculated, for example, using suitable methods such as, for example, the Sigmoid- $E_{\max}$ equation (Holford & Scheiner, 19981, Clin. Pharmacokinet. 6: 429-453), the equation of Loewe additivity (Loewe & Muischnek, 1926, Arch. Exp. Pathol Pharmacol. 114: 313-326) and the median-effect equation (Chou & Talalay, 1984, Adv. Enzyme Regul. 22: 27-55). Each equation referred to above may be applied to experimental data to generate a corresponding graph to aid in assessing the effects of the drug combination. The corresponding graphs associated with the equations referred to above are the concentration-effect curve, isobologram curve and combination index curve, respectively.

Methods of the Invention

The invention includes a method of preventing or treating a breathing control disorder or disease in a subject in need thereof. The method comprises administering to the subject an effective amount of a pharmaceutical formulation comprising at least one pharmaceutically acceptable carrier and at least one compound selected from the group consisting of: N-(2,4-bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine (CLXXII), N-(2,4,6-tris-*n*-propylamino)-[1,3,5]triazine (CLXXIII), N-(2,4,6-tris-*n*-propylamino)-1,3-pyrimidine (CLXXIV), N-(2,4-bis-*n*-propylamino)-N-(6-*i*-propylamino)-1,3-pyrimidine (CLXXV), a salt thereof, and any combinations thereof.

The invention also includes a method of preventing destabilization or stabilizing breathing rhythm in a subject in need thereof. The method comprises

administering to the subject an effective amount of a pharmaceutical formulation comprising at least one pharmaceutically acceptable carrier and at least one compound selected from the group consisting of: N-(2,4-bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine (CLXXII), N-(2,4,6-tris-*n*-propylamino)-[1,3,5]triazine (CLXXIII), N-(2,4,6-tris-*n*-propylamino)-1,3-pyrimidine (CLXXIV), N-(2,4-bis-*n*-propylamino)-N-(6-*i*-propylamino)-1,3-pyrimidine (CLXXV), a salt thereof, and any combinations thereof.

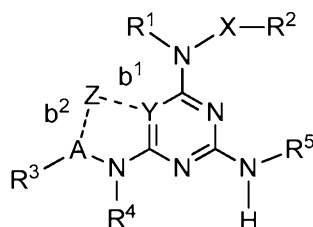
In one embodiment, the breathing control disorder or disease is selected from the group consisting of respiratory depression, sleep apnea, apnea of prematurity, obesity-hypoventilation syndrome, primary alveolar hypoventilation syndrome, dyspnea, hypoxia, and hypercapnia. In another embodiment, the respiratory depression is caused by an anesthetic, a sedative, an anxiolytic agent, a hypnotic agent, alcohol or a narcotic. In yet another embodiment, the subject is further administered a composition comprising at least one additional compound useful for treating the breathing control disorder or disease. In yet another embodiment, the at least one additional compound is selected from the group consisting of acetazolamide, almitrine, theophylline, caffeine, methyl progesterone, a serotonergic modulator, a cannabinoid and an ampakine. In yet another embodiment, the formulation is administered in conjunction with the use of a mechanical ventilation device or positive airway pressure device on the subject. In yet another embodiment, the subject is a mammal. In yet another embodiment, the mammal is a human. In yet another embodiment, the formulation is administered to the subject by an inhalational, topical, oral, buccal, rectal, vaginal, intramuscular, subcutaneous, transdermal, intrathecal or intravenous route.

The invention also includes a method of reducing or minimizing the open channel fraction of the potassium maxi-K or BK channel in a subject in need thereof. The method comprises administering to the subject an effective amount of a pharmaceutical formulation comprising at least one pharmaceutically acceptable carrier and at least one compound of formula (I).

The invention also includes a method of inhibiting the TASK-1 (KCNK3) channel in a subject in need thereof. The method comprises administering to the subject an effective amount of a pharmaceutical formulation comprising at least one pharmaceutically acceptable carrier and at least one compound of formula (I).

The invention also includes a method of increasing minute ventilation in a subject in need thereof. The method comprises administering to the subject an effective amount of a pharmaceutical formulation comprising at least one pharmaceutically acceptable carrier and at least one compound of formula (I).

5 In one embodiment, the compound of formula (I) is:



(I), wherein:

R^1 and R^2 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl; or R^1 and R^2 combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl; R^3 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-NR^1R^2$, $-C(O)OR^1$, acyl, or aryl; R^4 is H, alkyl, or substituted alkyl; R^5 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-OR^1$, $-NR^1R^2$, $-C(O)OR^1$, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, or substituted heterocyclic; or R^3 and R^5 combine as to form a biradical selected from the group consisting of 3,6,9-trioxa-undecane-1,11-diyl and 3,6-dioxa-octane-1,8-diyl; R^6 is H, alkyl, substituted alkyl or alkenyl; X is a bond, O or NR^4 ; and, Y is N, CR^6 or C; wherein:

if Y is N or CR^6 , then bond b^1 is nil and: (i) Z is H, bond b^2 is a single bond, and A is CH; or, (ii) Z is nil, bond b^2 is nil, and A is a single bond; and,

if Y is C, then bond b^1 is a single bond, and: (i) Z is CH_2 , bond b^2 is a single bond, and A is CH; or, (ii) Z is CH, bond b^2 is a double bond, and A is C; or a salt thereof.

In another embodiment, the compound of formula (I) is selected from the group consisting of: N-(4,6-Bis-methylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-ethylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-Cyclopropylmethyl)-N-(6-*n*-propylamino) [1,3,5]triazin-2-yl)-

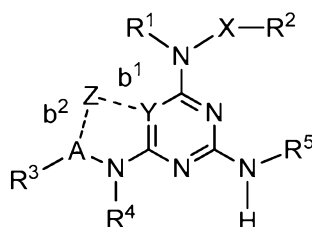
N,O-dimethyl-hydroxylamine, N-(4-Ethylamino)-N-(6-*n*-propylamino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2-methylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2,2-dimethylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2,2-dimethylpropylamino))[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-(Methoxy(methyl)amino)-6-(*n*-propylamino)-1,3,5-triazin-2-yl)propionamide, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-methyl-hydroxylamine, O-Allyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine, 6-(Methoxy(methyl)amino)-N²-propyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine, O-Benzyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-isopropyl-hydroxylamine, 6-[1,2]Oxazinan-2-yl-N,N'-dipropyl-[1,3,5]triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-N-methyl-hydroxylamine, O-Benzyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-hydroxylamine, 6-((Benzyloxy)(isopropyl) amino)-N²,N⁴-dipropyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-O-isopropyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isobutyl-N-methyl-hydroxylamine, 6-(Methyl(thiophen-2-ylmethoxy)amino)-N²,N⁴-dipropyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-cyclopropylmethyl-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-ethyl-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-(2,2-difluoro-ethyl)-hydroxylamine, 4-N-(2-Dimethylaminoethyl)amino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4-N-(3-(1-N-Methylimidazol-2-yl)-propyl)-amino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4-N-(1-N-Methylimidazol-2-yl)-methylamino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-(N-(2-dimethylaminoethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-(N-(pyridin-4-yl-methyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-[N-(3-methoxy-*n*-propyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-[N-(tetrahydropyran-4-yl-methyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(5,8,11-Trioxa-2,14,16,18,19-

pentaazabicyclo[13.3.1]nonadeca-1(18),15(19),16(17)-trien-17-yl)-N,O-
 dimethylhydroxylamine, 2,6-Bis-(N-*n*-propylamino)-[1,3]pyrimidin-4-yl)-N,O-
 dimethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N',N'-
 dimethylhydrazine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-N'-
 5 methylhydrazine, 2-(*n*-Propyl)amino-4-(*i*-propylamino-7-methyl-pyrrolidino[2,3-
 d]pyrimidine, 2-(*n*-Propyl)amino-4-dimethylamino-7-methyl-pyrrolidino[2,3-
 d]pyrimidine, 2-(*n*-Propyl)amino-4-methylamino-7-methyl-pyrrolidino[2,3-
 d]pyrimidine, 2-(*n*-Propyl)amino-4-(*i*-propyl)amino-7-*i*-propyl-pyrrolidino[2,3-
 d]pyrimidine, 2,4-Bis-(*n*-propyl)amino-7H-pyrrolidino[2,3-d]pyrimidine, 2-(*n*-
 10 Propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-methyl-pyrrolidino[2,3-d]pyrimidine, 8-
 (7-Methyl-2-(*n*-propylamino)-pyrrolidino[2,3-d]pyrimidin-4-yl)-8-
 azabicyclo[3.2.1]octan-3-ol, N-(2-Propylamino-7H-pyrrolo[2,3d]pyrimidin-4-yl)-
 N,O-dimethyl-hydroxylamine, N-(2-(Propen-2-yl)amino-7-methyl-
 pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-(Propen-2-
 15 yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine, N-(2-*n*-
 Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine,
 N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-
 hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-
 hydrazine, N-Methyl-N-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-
 20 hydrazine, N,N-Dimethyl-N'-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-
 yl)-hydrazine, N-(2,4-Bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine, N-
 (2,4,6-Tris-*n*-propylamino)-[1,3,5]triazine, N-(2,4,6-Tris-*n*-propylamino)-1,3-
 pyrimidine, N-(2,4-Bis-*n*-propylamino)-N-(6-*i*-propylamino)-1,3-pyrimidine, a salt
 thereof and mixtures thereof. In another embodiment, the compound of formula (I) is
 25 selected from the group consisting of: N-(4,6-Bis-*n*-propylamino-1,3,5]triazin-2-yl)-
 O-methyl-hydroxylamine; N-(4,6-Bis-*n*-propylamino-1,3,5]triazin-2-yl)-N',N'-
 dimethylhydrazine; N-(2,4-Bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine;
 N-[(2,6-Bis-*n*-propylamino)-pyrimidin-4-yl]-N,O-dimethyl-hydroxylamine; N,N-
 Dimethyl-N'-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine; a
 30 salt thereof and mixtures thereof. In yet another embodiment,

In one embodiment, the subject is a mammal. In another embodiment,
 the mammal is human. the compound of formula (I) is N-(4,6-Bis-*n*-propylamino-
 [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, or a salt thereof.

In one embodiment, the pharmaceutical formulation is administered via intravenous infusion. In another embodiment, the infusion dose of the pharmaceutical formulation is at least about 0.016 mg/kg/min. In yet another embodiment, the infusion dose of the pharmaceutical formulation is about 0.016 mg/kg/min. In yet another embodiment, the infusion dose of the pharmaceutical composition produces plasma concentrations of at least about 726 ng/mL in the subject. In yet another embodiment, the infusion dose of the pharmaceutical composition produces plasma concentrations of at least about 726 ng/mL in a mammal.

The present invention also includes a method of preventing or treating a breathing control disorder or disease in a subject in need thereof. The method includes administering to the subject an effective amount of a pharmaceutical formulation comprising at least a pharmaceutically acceptable carrier and at least one compound of formula (I):



(I), wherein

R^1 and R^2 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl; or R^1 and R^2 combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl; R^3 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-NR^1R^2$, $-C(O)OR^1$, acyl, or aryl; R^4 is H, alkyl, or substituted alkyl; R^5 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-OR^1$, $-NR^1R^2$, $-C(O)OR^1$, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, or substituted heterocyclic; or R^3 and R^5 combine as to form a biradical selected from the group consisting of 3,6,9-trioxa-undecane-1,11-diyl and 3,6-dioxa-octane-1,8-diyl; R^6 is H, alkyl, substituted alkyl or alkenyl; X is a bond, O or NR^4 ; and, Y is N, CR^6 or C;

wherein:

if Y is N or CR⁶, then bond b¹ is nil and: (i) Z is H, bond b² is a single bond, and A is CH; or, (ii) Z is nil, bond b² is nil, and A is a single bond; and,

if Y is C, then bond b¹ is a single bond, and: (i) Z is CH₂, bond b² is a single bond, and A is CH; or, (ii) Z is CH, bond b² is a double bond, and A is C; or a salt
5 thereof.

The present invention also includes a method of preventing destabilization of or stabilizing breathing rhythm in a subject in need thereof. The method includes administering to the subject an effective amount of a pharmaceutical formulation comprising at least a pharmaceutically acceptable carrier and at least one
10 compound of formula (I) or a salt thereof.

In one embodiment, administering the formulation of the invention stabilizes the breathing rhythm of the subject. In another embodiment, administering the formulation of the invention increases minute ventilation in the subject.

In one embodiment, the destabilization is associated with a breathing
15 control disorder or disease.

In one embodiment, the breathing disorder or disease is selected from the group consisting of narcotic-induced respiratory depression, anesthetic-induced respiratory depression, sedative-induced respiratory depression, anxiolytic-induced respiratory depression, hypnotic-induced respiratory depression, alcohol-induced
20 respiratory depression, analgesic-induced respiratory depression, sleep apnea, apnea of prematurity, obesity-hypoventilation syndrome, primary alveolar hypoventilation syndrome, dyspnea, altitude sickness, hypoxia, hypercapnia and chronic obstructive pulmonary disease (COPD). In another embodiment, the respiratory depression is caused by an anesthetic, a sedative, an anxiolytic agent, a hypnotic agent, alcohol or a
25 narcotic.

In one embodiment, the subject is further administered at least one additional compound useful for treating the breathing disorder or disease. In another embodiment, the at least one additional compound is selected from the group consisting of acetazolamide, almitrine, theophylline, caffeine, methylprogesterone and
30 related compounds, a serotonergic modulator, a cannabinoid, and an amphetamine. In yet another embodiment, the formulation is administered to the subject in conjunction with the use of a mechanical ventilation device or positive airway pressure device. In one embodiment, the formulation is administered to the subject by an inhalational, topical, oral, buccal, rectal, vaginal, intramuscular, subcutaneous, transdermal,

intrathecal or intravenous route. In another embodiment, the subject is a mammal including but not limited to mouse, rat, ferret, guinea pig, monkey, dog, cat, horse, cow, pig and other farm animals.

In one embodiment, the subject is a human. In another embodiment,

5 the at least one compound of formula (I) is selected from the group consisting of: N-(4,6-Bis-methylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-ethylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-Cyclopropylmethyl)-N-(6-*n*-propylamino) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-Ethylamino)-N-(6-*n*-propylamino)-[1,3,5]triazin-2-yl)-N,O-

10 dimethyl-hydroxylamine, N-(Bis-4,6-(2-methylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2,2-dimethylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2,2-dimethylpropylamino))[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-

15 (Methoxy(methyl)amino)-6-(*n*-propylamino)-1,3,5-triazin-2-yl)propionamide, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-methyl-hydroxylamine, O-Allyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine, 6-(Methoxy(methyl)amino)-N²-propyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-

20 hydroxylamine, O-Benzyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-isopropyl-hydroxylamine, 6-[1,2]Oxazinan-2-yl-N,N'-dipropyl-[1,3,5]triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-N-methyl-hydroxylamine, O-Benzyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-hydroxylamine, N-

25 (4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-hydroxylamine, 6-((Benzyloxy)(isopropyl) amino)-N²,N⁴-dipropyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-O-isopropyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isobutyl-N-methyl-hydroxylamine, 6-(Methyl(thiophen-2-ylmethoxy)amino)-N²,N⁴-dipropyl-1,3,5-triazine-2,4-diamine, N-

30 (4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-cyclopropylmethyl-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-ethyl-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-(2,2-difluoro-ethyl)-hydroxylamine, 4-N-(2-Dimethylaminoethyl)amino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4-N-(3-(1-N-Methylimidazol-2-yl)-

- propyl)-amino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4-N-(1-N-Methylimidazol-2-yl)-methylamino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-(N-(2-dimethylaminoethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-(N-(pyridin-4-yl-methyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-[N-(3-methoxy-*n*-propyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-[N-(tetrahydropyran-4-yl-methyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(5,8,11-Trioxa-2,14,16,18,19-pentaazabicyclo[13.3.1]nonadeca-1(18),15(19),16(17)-trien-17-yl)-N,O-dimethylhydroxylamine, 2,6-Bis-(N-*n*-propylamino)-[1,3]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N',N'-dimethylhydrazine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-N'-methylhydrazine, 2-(*n*-Propyl)amino-4-(*i*-propylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine, 2-(*n*-Propyl)amino-4-dimethylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine, 2-(*n*-Propyl)amino-4-methylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine, 2-(*n*-Propyl)amino-4-(*i*-propyl)amino-7-*i*-propyl-pyrrolidino[2,3-d]pyrimidine, 2,4-Bis-(*n*-propyl)amino-7H-pyrrolidino[2,3-d]pyrimidine, 2-(*n*-Propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-methyl-pyrrolidino[2,3-d]pyrimidine, 8-(7-Methyl-2-(*n*-propylamino)-pyrrolidino[2,3-d]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol, N-(2-Propylamino-7H-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine, N-Methyl-N-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine, N,N-Dimethyl-N'-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine, N-(2,4-Bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine, N-(2,4,6-Tris-*n*-propylamino)-[1,3,5]triazine, N-(2,4,6-Tris-*n*-propylamino)-1,3-pyrimidine, N-(2,4-Bis-*n*-propylamino)-N-(6-*i*-propylamino)-1,3-pyrimidine, a salt thereof and mixtures thereof.

Pharmaceutical Compositions and Formulations

The invention also encompasses the use of pharmaceutical compositions of at least one compound of the invention or a salt thereof to practice the methods of the invention.

5 Such a pharmaceutical composition may consist of at least one compound of the invention or a salt thereof, in a form suitable for administration to a subject, or the pharmaceutical composition may comprise at least one compound of the invention or a salt thereof, and one or more pharmaceutically acceptable carriers, one or more additional ingredients, or some combination of these. The at least one
10 compound of the invention may be present in the pharmaceutical composition in the form of a physiologically acceptable salt, such as in combination with a physiologically acceptable cation or anion, as is well known in the art.

 In an embodiment, the pharmaceutical compositions useful for practicing the method of the invention may be administered to deliver a dose of
15 between 1 ng/kg/day and 100 mg/kg/day. In another embodiment, the pharmaceutical compositions useful for practicing the invention may be administered to deliver a dose of between 1 ng/kg/day and 500 mg/kg/day.

 The relative amounts of the active ingredient, the pharmaceutically acceptable carrier, and any additional ingredients in a pharmaceutical composition of
20 the invention will vary, depending upon the identity, size, and condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

 Pharmaceutical compositions that are useful in the methods of the
25 invention may be suitably developed for inhalational, oral, rectal, vaginal, parenteral, topical, transdermal, pulmonary, intranasal, buccal, ophthalmic, intrathecal, intravenous or another route of administration. A composition useful within the methods of the invention may be directly administered to the brain, the brainstem, or any other part of the central nervous system of a mammal. Other contemplated
30 formulations include projected nanoparticles, liposomal preparations, resealed erythrocytes containing the active ingredient, and immunologically-based formulations. The route(s) of administration will be readily apparent to the skilled artisan and will depend upon any number of factors including the type and severity of

the disease being treated, the type and age of the veterinary or human patient being treated, and the like.

The formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of
5 pharmacology. In general, such preparatory methods include the step of bringing the active ingredient into association with a carrier or one or more other accessory ingredients, and then, if necessary or desirable, shaping or packaging the product into a desired single- or multi-dose unit.

As used herein, a “unit dose” is a discrete amount of the
10 pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient that would be administered to a subject or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage. The unit dosage form may be for a single daily dose or one of multiple daily doses (e.g., about
15 1 to 4 or more times per day). When multiple daily doses are used, the unit dosage form may be the same or different for each dose.

Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for ethical administration to humans, it will be understood by the skilled artisan that such
20 compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and perform such modification with merely ordinary, if any, experimentation. Subjects to
25 which administration of the pharmaceutical compositions of the invention is contemplated include, but are not limited to, humans and other primates, mammals including commercially relevant mammals such as cattle, pigs, horses, sheep, cats, and dogs.

In one embodiment, the compositions of the invention are formulated
30 using one or more pharmaceutically acceptable excipients or carriers. In one embodiment, the pharmaceutical compositions of the invention comprise a therapeutically effective amount of at least one compound of the invention and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers, which are useful, include, but are not limited to, glycerol, water, saline, ethanol and other

pharmaceutically acceptable salt solutions such as phosphates and salts of organic acids. Examples of these and other pharmaceutically acceptable carriers are described in Remington's Pharmaceutical Sciences (1991, Mack Publication Co., New Jersey).

The carrier may be a solvent or dispersion medium containing, for
5 example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms may be
10 achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions may be brought about by including in the composition
15 an agent that delays absorption, for example, aluminum monostearate or gelatin. In one embodiment, the pharmaceutically acceptable carrier is not DMSO alone.

Formulations may be employed in admixtures with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for oral, parenteral, nasal, inhalational, intravenous, subcutaneous,
20 transdermal enteral, or any other suitable mode of administration, known to the art. The pharmaceutical preparations may be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, coloring, flavoring and/or aromatic substances and the like. They may also be combined where desired with other active agents, e.g.,
25 other analgesic agents. As used herein, "additional ingredients" include, but are not limited to, one or more ingredients that may be used as a pharmaceutical carrier.

The composition of the invention may comprise a preservative from about 0.005% to 2.0% by total weight of the composition. The preservative is used to prevent spoilage in the case of exposure to contaminants in the environment.
30 Examples of preservatives useful in accordance with the invention included but are not limited to those selected from the group consisting of benzyl alcohol, sorbic acid, parabens, imidurea and combinations thereof. A particularly preferred preservative is a combination of about 0.5% to 2.0% benzyl alcohol and 0.05% to 0.5% sorbic acid.

The composition preferably includes an antioxidant and a chelating agent which inhibit the degradation of the compound. Preferred antioxidants for some compounds are BHT, BHA, alpha-tocopherol and ascorbic acid in the preferred range of about 0.01% to 0.3% and more preferably BHT in the range of 0.03% to 0.1% by weight by total weight of the composition. Preferably, the chelating agent is present in an amount of from 0.01% to 0.5% by weight by total weight of the composition. Particularly preferred chelating agents include edetate salts (e.g. disodium edetate) and citric acid in the weight range of about 0.01% to 0.20% and more preferably in the range of 0.02% to 0.10% by weight by total weight of the composition. The chelating agent is useful for chelating metal ions in the composition which may be detrimental to the shelf life of the formulation. While BHT and disodium edetate are the particularly preferred antioxidant and chelating agent respectively for some compounds, other suitable and equivalent antioxidants and chelating agents may be substituted therefore as would be known to those skilled in the art.

Liquid suspensions may be prepared using conventional methods to achieve suspension of the active ingredient in an aqueous or oily vehicle. Aqueous vehicles include, for example, water, and isotonic saline. Oily vehicles include, for example, almond oil, oily esters, ethyl alcohol, vegetable oils such as arachis, olive, sesame, or coconut oil, fractionated vegetable oils, and mineral oils such as liquid paraffin. Liquid suspensions may further comprise one or more additional ingredients including, but not limited to, suspending agents, dispersing or wetting agents, emulsifying agents, demulcents, preservatives, buffers, salts, flavorings, coloring agents, and sweetening agents. Oily suspensions may further comprise a thickening agent. Known suspending agents include, but are not limited to, sorbitol syrup, hydrogenated edible fats, sodium alginate, polyvinylpyrrolidone, gum tragacanth, gum acacia, and cellulose derivatives such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose. Known dispersing or wetting agents include, but are not limited to, naturally-occurring phosphatides such as lecithin, condensation products of an alkylene oxide with a fatty acid, with a long chain aliphatic alcohol, with a partial ester derived from a fatty acid and a hexitol, or with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene stearate, heptadecaethyleneoxycetanol, polyoxyethylene sorbitol monooleate, and polyoxyethylene sorbitan monooleate, respectively). Known emulsifying agents include, but are not limited to, lecithin, and acacia. Known preservatives include, but

are not limited to, methyl, ethyl, or *n*-propyl para-hydroxybenzoates, ascorbic acid, and sorbic acid. Known sweetening agents include, for example, glycerol, propylene glycol, sorbitol, sucrose, and saccharin. Known thickening agents for oily suspensions include, for example, beeswax, hard paraffin, and cetyl alcohol.

5 Liquid solutions of the active ingredient in aqueous or oily solvents may be prepared in substantially the same manner as liquid suspensions, the primary difference being that the active ingredient is dissolved, rather than suspended in the solvent. As used herein, an “oily” liquid is one which comprises a carbon-containing liquid molecule and which exhibits a less polar character than water. Liquid solutions
10 of the pharmaceutical composition of the invention may comprise each of the components described with regard to liquid suspensions, it being understood that suspending agents will not necessarily aid dissolution of the active ingredient in the solvent. Aqueous solvents include, for example, water, and isotonic saline. Oily solvents include, for example, almond oil, oily esters, ethyl alcohol, vegetable oils
15 such as arachis, olive, sesame, or coconut oil, fractionated vegetable oils, and mineral oils such as liquid paraffin.

Powdered and granular formulations of a pharmaceutical preparation of the invention may be prepared using known methods. Such formulations may be administered directly to a subject, used, for example, to form tablets, to fill capsules,
20 or to prepare an aqueous or oily suspension or solution by addition of an aqueous or oily vehicle thereto. Each of these formulations may further comprise one or more of dispersing or wetting agent, a suspending agent, and a preservative. Additional excipients, such as fillers and sweetening, flavoring, or coloring agents, may also be included in these formulations.

25 A pharmaceutical composition of the invention may also be prepared, packaged, or sold in the form of oil-in-water emulsion or a water-in-oil emulsion. The oily phase may be a vegetable oil such as olive or arachis oil, a mineral oil such as liquid paraffin, or a combination of these. Such compositions may further comprise one or more emulsifying agents such as naturally occurring gums such as
30 gum acacia or gum tragacanth, naturally-occurring phosphatides such as soybean or lecithin phosphatide, esters or partial esters derived from combinations of fatty acids and hexitol anhydrides such as sorbitan monooleate, and condensation products of such partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate.

These emulsions may also contain additional ingredients including, for example, sweetening or flavoring agents.

Methods for impregnating or coating a material with a chemical composition are known in the art, and include, but are not limited to methods of depositing or binding a chemical composition onto a surface, methods of incorporating a chemical composition into the structure of a material during the synthesis of the material (i.e., such as with a physiologically degradable material), and methods of absorbing an aqueous or oily solution or suspension into an absorbent material, with or without subsequent drying.

10

Administration/Dosing

The regimen of administration may affect what constitutes an effective amount. The therapeutic formulations may be administered to the patient either prior to or after the onset of a breathing disorder event. Further, several divided dosages, as well as staggered dosages may be administered daily or sequentially, or the dose may be continuously infused, or may be a bolus injection. Further, the dosages of the therapeutic formulations may be proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.

Administration of the compositions of the present invention to a patient, preferably a mammal or avian, more preferably a human, may be carried out using known procedures, at dosages and for periods of time effective to treat a breathing control disorder in the patient. An effective amount of the therapeutic compound necessary to achieve a therapeutic effect may vary according to factors such as the activity of the particular compound employed; the time of administration; the rate of excretion of the compound; the duration of the treatment; other drugs, compounds or materials used in combination with the compound; the state of the disease or disorder, age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well-known in the medical arts. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A non-limiting example of an effective dose range for a therapeutic compound of the invention is from about 0.01 mg/kg and 50 mg/kg of body weight/per day. One of ordinary skill in the art would be able to study the relevant factors and make the

determination regarding the effective amount of the therapeutic compound without undue experimentation.

The compound can be administered to an animal as frequently as several times daily, or it may be administered less frequently, such as once a day, 5 once a week, once every two weeks, once a month, or even less frequently, such as once every several months or even once a year or less. It is understood that the amount of compound dosed per day may be administered, in non-limiting examples, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days. For example, with every other day administration, a 5 mg per day dose may be 10 initiated on Monday with a first subsequent 5 mg per day dose administered on Wednesday, a second subsequent 5 mg per day dose administered on Friday, and so on. The frequency of the dose will be readily apparent to the skilled artisan and will depend upon any number of factors, such as, but not limited to, the type and severity of the disease being treated, the type and age of the animal, etc.

15 Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

A medical doctor, e.g., physician or veterinarian, having ordinary skill 20 in the art may readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is 25 achieved.

In particular embodiments, it is especially advantageous to formulate the compound in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the patients to be treated; each unit containing a predetermined 30 quantity of therapeutic compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the therapeutic compound and the particular therapeutic effect to be achieved, and (b)

the limitations inherent in the art of compounding/formulating such a therapeutic compound for the treatment of breathing disorders in a patient.

In one embodiment, the compositions of the invention are administered to the patient in dosages that range from one to five times per day or more. In another
5 embodiment, the compositions of the invention are administered to the patient in range of dosages that include, but are not limited to, once every day, every two, days, every three days to once a week, and once every two weeks. It will be readily apparent to one skilled in the art that the frequency of administration of the various combination compositions of the invention will vary from subject to subject
10 depending on many factors including, but not limited to, age, disease or disorder to be treated, gender, overall health, and other factors. Thus, the invention should not be construed to be limited to any particular dosage regime and the precise dosage and composition to be administered to any patient will be determined by the attending physical taking all other factors about the patient into account.

15 Compounds of the invention for administration may be in the range of from about 1 μ g to about 7,500 mg, about 20 μ g to about 7,000 mg, about 40 μ g to about 6,500 mg, about 80 μ g to about 6,000 mg, about 100 μ g to about 5,500 mg, about 200 μ g to about 5,000 mg, about 400 μ g to about 4,000 mg, about 800 μ g to about 3,000 mg, about 1 mg to about 2,500 mg, about 2 mg to about 2,000 mg, about
20 5 mg to about 1,000 mg, about 10 mg to about 750 mg, about 20 mg to about 600 mg, about 30 mg to about 500 mg, about 40 mg to about 400 mg, about 50 mg to about 300 mg, about 60 mg to about 250 mg, about 70 mg to about 200 mg, about 80 mg to about 150 mg, and any and all whole or partial increments thereinbetween.

In some embodiments, the dose of a compound of the invention is from
25 about 0.5 μ g and about 5,000 mg. In some embodiments, a dose of a compound of the invention used in compositions described herein is less than about 5,000 mg, or less than about 4,000 mg, or less than about 3,000 mg, or less than about 2,000 mg, or less than about 1,000 mg, or less than about 800 mg, or less than about 600 mg, or less than about 500 mg, or less than about 200 mg, or less than about 50 mg.
30 Similarly, in some embodiments, a dose of a second compound as described herein is less than about 1,000 mg, or less than about 800 mg, or less than about 600 mg, or less than about 500 mg, or less than about 400 mg, or less than about 300 mg, or less than about 200 mg, or less than about 100 mg, or less than about 50 mg, or less than

about 40 mg, or less than about 30 mg, or less than about 25 mg, or less than about 20 mg, or less than about 15 mg, or less than about 10 mg, or less than about 5 mg, or less than about 2 mg, or less than about 1 mg, or less than about 0.5 mg, and any and all whole or partial increments thereof.

5 In one embodiment, the present invention is directed to a packaged pharmaceutical composition comprising a container holding a therapeutically effective amount of a compound of the invention, alone or in combination with a second pharmaceutical agent; and instructions for using the compound to treat, prevent, or reduce one or more symptoms of breathing disorder in a patient.

10 The term "container" includes any receptacle for holding the pharmaceutical composition. For example, in one embodiment, the container is the packaging that contains the pharmaceutical composition. In other embodiments, the container is not the packaging that contains the pharmaceutical composition, i.e., the container is a receptacle, such as a box or vial that contains the packaged
15 pharmaceutical composition or unpackaged pharmaceutical composition and the instructions for use of the pharmaceutical composition. Moreover, packaging techniques are well known in the art. It should be understood that the instructions for use of the pharmaceutical composition may be contained on the packaging containing the pharmaceutical composition, and as such the instructions form an increased
20 functional relationship to the packaged product. However, it should be understood that the instructions may contain information pertaining to the compound's ability to perform its intended function, e.g., treating, preventing, or reducing a breathing disorder in a patient.

25 Routes of Administration

 Routes of administration of any of the compositions of the invention include inhalational, oral, nasal, rectal, parenteral, sublingual, transdermal, transmucosal (*e.g.*, sublingual, lingual, (trans)buccal, (trans)urethral, vaginal (*e.g.*, trans- and perivaginally), (intra)nasal, and (trans)rectal), intravesical, intrapulmonary,
30 intraduodenal, intragastrical, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, intraperitoneal, intrathoracic, intrapleural and topical administration.

 Suitable compositions and dosage forms include, for example, tablets, capsules, caplets, pills, gel caps, troches, dispersions, suspensions, solutions, syrups,

granules, beads, transdermal patches, gels, powders, pellets, magmas, lozenges, creams, pastes, plasters, lotions, discs, suppositories, liquid sprays for nasal or oral administration, dry powder or aerosolized formulations for inhalation, compositions and formulations for intravesical administration and the like. It should be understood
5 that the formulations and compositions that would be useful in the present invention are not limited to the particular formulations and compositions that are described herein.

Oral Administration

For oral application, particularly suitable are tablets, dragees, liquids,
10 drops, suppositories, or capsules, caplets and gelcaps. Other formulations suitable for oral administration include, but are not limited to, a powdered or granular formulation, an aqueous or oily suspension, an aqueous or oily solution, a paste, a gel, toothpaste, a mouthwash, a coating, an oral rinse, or an emulsion. The compositions intended for oral use may be prepared according to any method known in the art and
15 such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically excipients which are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate.

20 Tablets may be non-coated or they may be coated using known methods to achieve delayed disintegration in the gastrointestinal tract of a subject, thereby providing sustained release and absorption of the active ingredient. By way of example, a material such as glyceryl monostearate or glyceryl distearate may be used to coat tablets. Further by way of example, tablets may be coated using methods
25 described in U.S. Patents Nos. 4,256,108; 4,160,452; and 4,265,874 to form osmotically controlled release tablets. Tablets may further comprise a sweetening agent, a flavoring agent, a coloring agent, a preservative, or some combination of these in order to provide for pharmaceutically elegant and palatable preparation.

Hard capsules comprising the active ingredient may be made using a
30 physiologically degradable composition, such as gelatin. Such hard capsules comprise the active ingredient, and may further comprise additional ingredients including, for example, an inert solid diluent such as calcium carbonate, calcium phosphate, or kaolin.

Soft gelatin capsules comprising the active ingredient may be made using a physiologically degradable composition, such as gelatin. Such soft capsules comprise the active ingredient, which may be mixed with water or an oil medium such as peanut oil, liquid paraffin, or olive oil.

5 For oral administration, the compounds of the invention may be in the form of tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents; fillers; lubricants; disintegrates; or wetting agents. If desired, the tablets may be coated using suitable methods and coating materials such as OPADRY™ film coating systems available from Colorcon,
10 West Point, Pa. (e.g., OPADRY™ OY Type, OYC Type, Organic Enteric OY-P Type, Aqueous Enteric OY-A Type, OY-PM Type and OPADRY™ White, 32K18400).

Liquid preparation for oral administration may be in the form of solutions, syrups or suspensions. The liquid preparations may be prepared by
15 conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agent (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl para-hydroxy benzoates or sorbic acid). Liquid formulations of a pharmaceutical composition of the invention
20 which are suitable for oral administration may be prepared, packaged, and sold either in liquid form or in the form of a dry product intended for reconstitution with water or another suitable vehicle prior to use.

A tablet comprising the active ingredient may, for example, be made by compressing or molding the active ingredient, optionally with one or more
25 additional ingredients. Compressed tablets may be prepared by compressing, in a suitable device, the active ingredient in a free-flowing form such as a powder or granular preparation, optionally mixed with one or more of a binder, a lubricant, an excipient, a surface active agent, and a dispersing agent. Molded tablets may be made by molding, in a suitable device, a mixture of the active ingredient, a
30 pharmaceutically acceptable carrier, and at least sufficient liquid to moisten the mixture. Pharmaceutically acceptable excipients used in the manufacture of tablets include, but are not limited to, inert diluents, granulating and disintegrating agents, binding agents, and lubricating agents. Known dispersing agents include, but are not limited to, potato starch and sodium starch glycollate. Known surface-active agents

include, but are not limited to, sodium lauryl sulphate. Known diluents include, but are not limited to, calcium carbonate, sodium carbonate, lactose, microcrystalline cellulose, calcium phosphate, calcium hydrogen phosphate, and sodium phosphate. Known granulating and disintegrating agents include, but are not limited to, corn starch and alginic acid. Known binding agents include, but are not limited to, gelatin, acacia, pre-gelatinized maize starch, polyvinylpyrrolidone, and hydroxypropyl methylcellulose. Known lubricating agents include, but are not limited to, magnesium stearate, stearic acid, silica, and talc.

Granulating techniques are well known in the pharmaceutical art for modifying starting powders or other particulate materials of an active ingredient. The powders are typically mixed with a binder material into larger permanent free-flowing agglomerates or granules referred to as a “granulation.” For example, solvent-using “wet” granulation processes are generally characterized in that the powders are combined with a binder material and moistened with water or an organic solvent under conditions resulting in the formation of a wet granulated mass from which the solvent must then be evaporated.

Melt granulation generally consists in the use of materials that are solid or semi-solid at room temperature (i.e. having a relatively low softening or melting point range) to promote granulation of powdered or other materials, essentially in the absence of added water or other liquid solvents. The low melting solids, when heated to a temperature in the melting point range, liquefy to act as a binder or granulating medium. The liquefied solid spreads itself over the surface of powdered materials with which it is contacted, and on cooling, forms a solid granulated mass in which the initial materials are bound together. The resulting melt granulation may then be provided to a tablet press or be encapsulated for preparing the oral dosage form. Melt granulation improves the dissolution rate and bioavailability of an active (i.e. drug) by forming a solid dispersion or solid solution.

U.S. Patent No. 5,169,645 discloses directly compressible wax-containing granules having improved flow properties. The granules are obtained when waxes are admixed in the melt with certain flow improving additives, followed by cooling and granulation of the admixture. In certain embodiments, only the wax itself melts in the melt combination of the wax(es) and additives(s), and in other cases both the wax(es) and the additives(s) will melt.

The present invention also includes a multi-layer tablet comprising a layer providing for the delayed release of one or more compounds useful within the methods of the invention, and a further layer providing for the immediate release of one or more compounds useful within the methods of the invention. Using a wax/pH-sensitive polymer mix, a gastric insoluble composition may be obtained in which the active ingredient is entrapped, ensuring its delayed release.

Parenteral Administration

As used herein, "parenteral administration" of a pharmaceutical composition includes any route of administration characterized by physical breaching of a tissue of a subject and administration of the pharmaceutical composition through the breach in the tissue. Parenteral administration thus includes, but is not limited to, administration of a pharmaceutical composition by injection of the composition, by application of the composition through a surgical incision, by application of the composition through a tissue-penetrating non-surgical wound, and the like. In particular, parenteral administration is contemplated to include, but is not limited to, subcutaneous, intravenous, intraperitoneal, intramuscular, intrasternal injection, and kidney dialytic infusion techniques.

Formulations of a pharmaceutical composition suitable for parenteral administration comprise the active ingredient combined with a pharmaceutically acceptable carrier, such as sterile water or sterile isotonic saline. Such formulations may be prepared, packaged, or sold in a form suitable for bolus administration or for continuous administration. Injectable formulations may be prepared, packaged, or sold in unit dosage form, such as in ampules or in multi-dose containers containing a preservative. Formulations for parenteral administration include, but are not limited to, suspensions, solutions, emulsions in oily or aqueous vehicles, pastes, and implantable sustained-release or biodegradable formulations. Such formulations may further comprise one or more additional ingredients including, but not limited to, suspending, stabilizing, or dispersing agents. In one embodiment of a formulation for parenteral administration, the active ingredient is provided in dry (i.e., powder or granular) form for reconstitution with a suitable vehicle (e.g., sterile pyrogen-free water) prior to parenteral administration of the reconstituted composition.

The pharmaceutical compositions may be prepared, packaged, or sold in the form of a sterile injectable aqueous or oily suspension or solution. This suspension or solution may be formulated according to the known art, and may

comprise, in addition to the active ingredient, additional ingredients such as the dispersing agents, wetting agents, or suspending agents described herein. Such sterile injectable formulations may be prepared using a non-toxic parenterally-acceptable diluent or solvent, such as water or 1,3-butane diol, for example. Other acceptable
5 diluents and solvents include, but are not limited to, Ringer's solution, isotonic sodium chloride solution, and fixed oils such as synthetic mono- or di-glycerides. Other parentally-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form, in a liposomal preparation, or as a component of a biodegradable polymer system. Compositions for sustained
10 release or implantation may comprise pharmaceutically acceptable polymeric or hydrophobic materials such as an emulsion, an ion exchange resin, a sparingly soluble polymer, or a sparingly soluble salt.

Topical Administration

An obstacle for topical administration of pharmaceuticals is the
15 stratum corneum layer of the epidermis. The stratum corneum is a highly resistant layer comprised of protein, cholesterol, sphingolipids, free fatty acids and various other lipids, and includes cornified and living cells. One of the factors that limit the penetration rate (flux) of a compound through the stratum corneum is the amount of the active substance that can be loaded or applied onto the skin surface. The greater
20 the amount of active substance which is applied per unit of area of the skin, the greater the concentration gradient between the skin surface and the lower layers of the skin, and in turn the greater the diffusion force of the active substance through the skin. Therefore, a formulation containing a greater concentration of the active substance is more likely to result in penetration of the active substance through the
25 skin, and more of it, and at a more consistent rate, than a formulation having a lesser concentration, all other things being equal.

Formulations suitable for topical administration include, but are not limited to, liquid or semi-liquid preparations such as liniments, lotions, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes, and solutions or
30 suspensions. Topically administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient may be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

Enhancers of permeation may be used. These materials increase the rate of penetration of drugs across the skin. Typical enhancers in the art include ethanol, glycerol monolaurate, PGML (polyethylene glycol monolaurate), dimethylsulfoxide, and the like. Other enhancers include oleic acid, oleyl alcohol, ethoxydiglycol, laurocapram, alkanecarboxylic acids, dimethylsulfoxide, polar lipids, or N-methyl-2-pyrrolidone.

One acceptable vehicle for topical delivery of some of the compositions of the invention may contain liposomes. The composition of the liposomes and their use are known in the art (for example, see Constanza, U.S. Patent No. 6,323,219).

In alternative embodiments, the topically active pharmaceutical composition may be optionally combined with other ingredients such as adjuvants, anti-oxidants, chelating agents, surfactants, foaming agents, wetting agents, emulsifying agents, viscosifiers, buffering agents, preservatives, and the like. In another embodiment, a permeation or penetration enhancer is included in the composition and is effective in improving the percutaneous penetration of the active ingredient into and through the stratum corneum with respect to a composition lacking the permeation enhancer. Various permeation enhancers, including oleic acid, oleyl alcohol, ethoxydiglycol, laurocapram, alkanecarboxylic acids, dimethylsulfoxide, polar lipids, or N-methyl-2-pyrrolidone, are known to those of skill in the art. In another aspect, the composition may further comprise a hydrotropic agent, which functions to increase disorder in the structure of the stratum corneum, and thus allows increased transport across the stratum corneum. Various hydrotropic agents such as isopropyl alcohol, propylene glycol, or sodium xylene sulfonate, are known to those of skill in the art.

The topically active pharmaceutical composition should be applied in an amount effective to affect desired changes. As used herein "amount effective" shall mean an amount sufficient to cover the region of skin surface where a change is desired. An active compound should be present in the amount of from about 0.0001% to about 15% by weight volume of the composition. More preferable, it should be present in an amount from about 0.0005% to about 5% of the composition; most preferably, it should be present in an amount of from about 0.001% to about 1% of the composition. Such compounds may be synthetically-or naturally derived.

Buccal Administration

A pharmaceutical composition of the invention may be prepared, packaged, or sold in a formulation suitable for buccal administration. Such formulations may, for example, be in the form of tablets or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) of the active ingredient, the balance comprising an orally dissolvable or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations suitable for buccal administration may comprise a powder or an aerosolized or atomized solution or suspension comprising the active ingredient. Such powdered, aerosolized, or aerosolized formulations, when dispersed, preferably have an average particle or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein. The examples of formulations described herein are not exhaustive and it is understood that the invention includes additional modifications of these and other formulations not described herein, but which are known to those of skill in the art.

Rectal Administration

A pharmaceutical composition of the invention may be prepared, packaged, or sold in a formulation suitable for rectal administration. Such a composition may be in the form of, for example, a suppository, a retention enema preparation, and a solution for rectal or colonic irrigation.

Suppository formulations may be made by combining the active ingredient with a non-irritating pharmaceutically acceptable excipient which is solid at ordinary room temperature (i.e., about 20°C) and which is liquid at the rectal temperature of the subject (i.e., about 37°C in a healthy human). Suitable pharmaceutically acceptable excipients include, but are not limited to, cocoa butter, polyethylene glycols, and various glycerides. Suppository formulations may further comprise various additional ingredients including, but not limited to, antioxidants, and preservatives.

Retention enema preparations or solutions for rectal or colonic irrigation may be made by combining the active ingredient with a pharmaceutically acceptable liquid carrier. As is well known in the art, enema preparations may be administered using, and may be packaged within, a delivery device adapted to the

rectal anatomy of the subject. Enema preparations may further comprise various additional ingredients including, but not limited to, antioxidants, and preservatives.

Additional Administration Forms

Additional dosage forms of this invention include dosage forms as described in U.S. Patents Nos. 6,340,475, 6,488,962, 6,451,808, 5,972,389, 5,582,837, and 5,007,790. Additional dosage forms of this invention also include dosage forms as described in U.S. Patent Applications Nos. 20030147952, 20030104062, 20030104053, 20030044466, 20030039688, and 20020051820. Additional dosage forms of this invention also include dosage forms as described in PCT Applications Nos. WO 03/35041, WO 03/35040, WO 03/35029, WO 03/35177, WO 03/35039, WO 02/96404, WO 02/32416, WO 01/97783, WO 01/56544, WO 01/32217, WO 98/55107, WO 98/11879, WO 97/47285, WO 93/18755, and WO 90/11757.

15 Controlled Release Formulations and Drug Delivery Systems

Controlled- or sustained-release formulations of a pharmaceutical composition of the invention may be made using conventional technology. In some cases, the dosage forms to be used can be provided as slow or controlled-release of one or more active ingredients therein using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the pharmaceutical compositions of the invention. Thus, single unit dosage forms suitable for oral administration, such as tablets, capsules, gelcaps, and caplets, that are adapted for controlled-release are encompassed by the present invention.

Most controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be

used to affect the time of onset of action or other characteristics, such as blood level of the drug, and thus can affect the occurrence of side effects.

Most controlled-release formulations are designed to initially release an amount of drug that promptly produces the desired therapeutic effect, and
5 gradually and continually release of other amounts of drug to maintain this level of therapeutic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body.

Controlled-release of an active ingredient can be stimulated by various
10 inducers, for example pH, temperature, enzymes, water, or other physiological conditions or compounds. The term "controlled-release component" in the context of the present invention is defined herein as a compound or compounds, including, but not limited to, polymers, polymer matrices, gels, permeable membranes, liposomes, or microspheres or a combination thereof that facilitates the controlled-release of the
15 active ingredient.

In certain embodiments, the formulations of the present invention may be, but are not limited to, short-term, rapid-offset, as well as controlled, for example, sustained release, delayed release and pulsatile release formulations.

The term sustained release is used in its conventional sense to refer to a
20 drug formulation that provides for gradual release of a drug over an extended period of time, and that may, although not necessarily, result in substantially constant blood levels of a drug over an extended time period. The period of time may be as long as a month or more and should be a release that is longer than the same amount of agent administered in bolus form.

25 For sustained release, the compounds may be formulated with a suitable polymer or hydrophobic material which provides sustained release properties to the compounds. As such, the compounds for use the method of the invention may be administered in the form of microparticles, for example, by injection or in the form of wafers or discs by implantation.

30 In a preferred embodiment of the invention, the compounds of the invention are administered to a patient, alone or in combination with another pharmaceutical agent, using a sustained release formulation.

The term delayed release is used herein in its conventional sense to refer to a drug formulation that provides for an initial release of the drug after some

delay following drug administration and that may, although not necessarily, includes a delay of from about 10 minutes up to about 12 hours.

The term pulsatile release is used herein in its conventional sense to refer to a drug formulation that provides release of the drug in such a way as to
5 produce pulsed plasma profiles of the drug after drug administration.

The term immediate release is used in its conventional sense to refer to a drug formulation that provides for release of the drug immediately after drug administration.

As used herein, short-term refers to any period of time up to and
10 including about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 40 minutes, about 20 minutes, or about 10 minutes and any or all whole or partial increments thereof after drug administration after drug administration.

As used herein, rapid-offset refers to any period of time up to and
15 including about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 40 minutes, about 20 minutes, or about 10 minutes, and any and all whole or partial increments thereof after drug administration.

20 Mechanical Devices

In one aspect of the invention, a method of treating a patient lacking normal breathing and normal breathing control comprises administering the composition useful within the invention as described herein, and additionally treating the patient using a device for treatment of a lack of normal breathing. Such devices
25 include, but are not limited to, ventilation devices, CPAP and BiPAP devices.

Mechanical ventilation is a method to mechanically assist or replace spontaneous breathing. Mechanical ventilation is typically used after an invasive intubation, a procedure wherein an endotracheal or tracheostomy tube is inserted into the airway. It is normally used in acute settings, such as in the operating room or
30 ICU, for a short period of time during surgery, medical procedure, or serious illness. It may also be used at home or in a nursing or rehabilitation institution, if patients have chronic illnesses that require long-term ventilation assistance. The main form of mechanical ventilation is positive pressure ventilation, which works by increasing the pressure in the patient's airway and thus forcing air into the lungs. Less common

today are negative pressure ventilators (for example, the "iron lung") that create a negative pressure environment around the patient's chest, thus sucking air into the lungs. Mechanical ventilation is often a life-saving intervention, but carries many potential complications including pneumothorax, airway injury, alveolar damage, and ventilator-associated pneumonia. For this reason the pressure and volume of gas used is strictly controlled, and reduced as soon as possible. Types of mechanical ventilation are: conventional ventilation, high frequency ventilation, non-invasive ventilation (non-invasive positive pressure ventilation or NIPPV), proportional assist ventilation (PAV), adaptive support ventilation (ASV) and neurally adjusted ventilatory assist (NAVA).

Non-invasive ventilation refers to all modalities that assist ventilation without the use of an endotracheal tube. Non-invasive ventilation is primarily aimed at minimizing patient discomfort and the complications associated with invasive ventilation, and is often used in cardiac disease, exacerbations of chronic pulmonary disease, sleep apnea, and neuromuscular diseases. Non-invasive ventilation refers only to the patient interface and not the mode of ventilation used; modes may include spontaneous or control modes and may be either pressure or volume modes. Some commonly used modes of NIPPV include:

(a) Continuous positive airway pressure (CPAP): This kind of machine has been used mainly by patients for the treatment of sleep apnea at home, but now is in widespread use across intensive care units as a form of ventilation. The CPAP machine stops upper airway obstruction by delivering a stream of compressed air via a hose to a nasal pillow, nose mask or full-face mask, splinting the airway (keeping it open under air pressure) so that unobstructed breathing becomes possible, reducing and/or preventing apneas and hypopneas. When the machine is turned on, but prior to the mask being placed on the head, a flow of air comes through the mask. After the mask is placed on the head, it is sealed to the face and the air stops flowing. At this point, it is only the air pressure that accomplishes the desired result. This has the additional benefit of reducing or eliminating the extremely loud snoring that sometimes accompanies sleep apnea.

(b) Bi-level positive airway pressure (BIPAP): Pressures alternate between inspiratory positive airway pressure (IPAP) and a lower expiratory positive airway pressure (EPAP), triggered by patient effort. On many such devices, backup rates may be set, which deliver IPAP pressures even if patients fail to initiate a breath.

(c) Intermittent positive pressure ventilation (IPPV), via mouthpiece or mask.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures, embodiments, claims, and examples described herein. Such equivalents were
5 considered to be within the scope of this invention and covered by the claims appended hereto. For example, it should be understood, that modifications in reaction conditions, including but not limited to reaction times, reaction size/volume, and experimental reagents, such as solvents, catalysts, pressures, atmospheric conditions, e.g., nitrogen atmosphere, and reducing/oxidizing agents, with art-recognized
10 alternatives and using no more than routine experimentation, are within the scope of the present application.

It is to be understood that, wherever values and ranges are provided herein, the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention.
15 Accordingly, all values and ranges encompassed by these values and ranges are meant to be encompassed within the scope of the present invention. Moreover, all values that fall within these ranges, as well as the upper or lower limits of a range of values, are also contemplated by the present application. The description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as
20 individual numerical values within that range and, when appropriate, partial integers of the numerical values within ranges. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed sub-ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6.
25 This applies regardless of the breadth of the range.

The following examples further illustrate aspects of the present invention. However, they are in no way a limitation of the teachings or disclosure of the present invention as set forth herein.

30

EXAMPLES

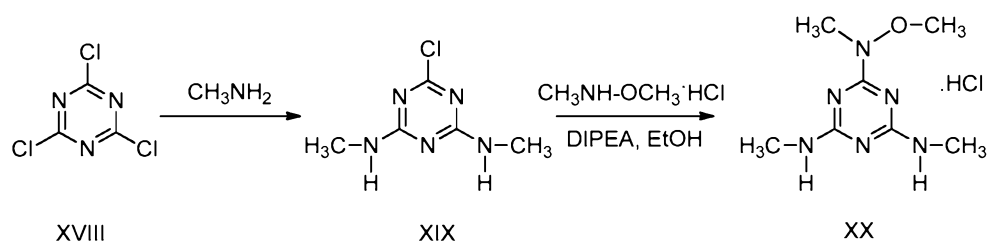
The invention is now described with reference to the following Examples. These Examples are provided for the purpose of illustration only, and the invention is not limited to these Examples, but rather encompasses all variations that are evident as a result of the teachings provided herein.

Materials:

Unless otherwise noted, all remaining starting materials were obtained from commercial suppliers and used without purification. Final products are typically isolated as hydrochloride acid addition salts unless noted otherwise.

Example 1:

N-(4,6-Bis-methylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (XX)



10

Scheme 8*2-Chloro-N-(4,6-bis-methylamino)-[1,3,5]triazine (XIX)*

2,4,6-Trichloro-1,3,5-triazine (XVIII) (5.0 g, 27 mmol) was dissolved in acetone (35 mL) and poured into ice-water (50 mL) to form a very fine suspension. A solution of N-methylamine hydrochloride (3.66 g, 54 mmol) in water (20 mL) was added and the temperature maintained at approximately 0 °C. To this mixture, 2N NaOH (54 mL, 108 mmol) was added in a dropwise manner to keep the temperature between 0 °C and 5 °C. The mixture was stirred 30 min at ambient temperature for an additional 60 min at 50 °C. The precipitate was filtered and washed with water (3 x 25 mL). After drying over anhydrous calcium chloride under high vacuum, 2-chloro-N-(4,6-bis-methylamino)-[1,3,5]triazine (XIX) was isolated as a white powder (4.2 g, 89% yield). LCMS (ESI) m/z = 174 (M+H)⁺.

N-(4,6-Bis-methylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (XX)

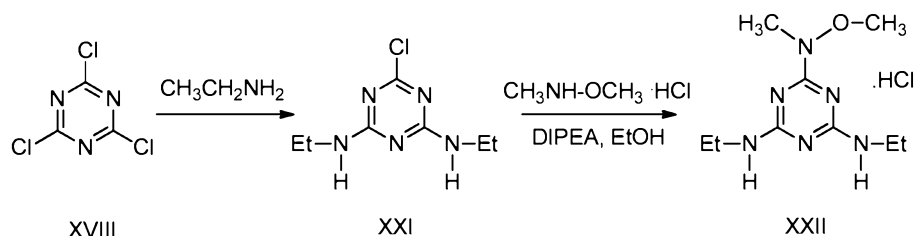
A mixture of 2-chloro-N-(4,6-bis-methylamino)-[1,3,5]triazine (XIX) (1.74 g, 10 mmol), N,O-dimethylhydroxylamine hydrochloride (3.88 g, 40 mmol) and DIPEA (7.74 g, 60 mmol) in EtOH (200 mL) was heated at 100 °C for 16 h, after

which the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (150 mL), washed with water (100 mL) and brine solution (100 mL), and then dried over Na₂SO₄. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (pet ether/ethyl acetate = 5/1 to 5/3) to yield 899 mg (23%) of the desired product. The isolated free amine (380 mg, 2 mmol) was placed into H₂O (10 mL) and 0.5 M aqueous HCl solution (6 mL) was added. The resultant solution was subjected to lyophilization to yield the desired product, N-(4,6-bis-methylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (XX), as a white solid (468 mg). LCMS (ESI) m/z = 199 (M+H)⁺. ¹H NMR (500 MHz, DMSO): δ (ppm) 12.20-12.50 (br, 1H), 8.48-8.62 (m, 2H), 3.76-3.86 (m, 3H), 3.29-3.39 (m, 3H), 2.76-2.93 (m, 6H).

Example 2:

N-(4,6-Bis-ethylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine

15 hydrochloride (XXII)



Scheme 9

2-Chloro-N-(4, 6-bis-ethylamino)-[1,3,5]triazine (XXI)

20 2,4,6-Trichloro-1,3,5-triazine (XVIII) (5.0 g, 27 mmol) was dissolved in acetone (35 mL) and poured into ice-water (50 mL) to form a very fine suspension. A solution of ethylamine (2.43 g, 54 mmol) in water (20 mL) was added and the temperature maintained at approximately 0 °C. To this mixture, 2N NaOH (27 mL, 54 mmol) was added in a dropwise manner to keep the temperature between 0 °C and 25 °C. The mixture was stirred for 30 min at ambient temperature, and for additional 60 min at 50 °C. The precipitate was filtered off, washed with water (3 x 25 mL). After drying over anhydrous calcium chloride under high vacuum, 2-chloro-N-(4, 6-bis-ethylamino)-[1,3,5]triazine (XXI) was isolated as a white powder (5.0 g, 92% yield). LCMS (ESI) m/z = 202 (M+H)⁺.

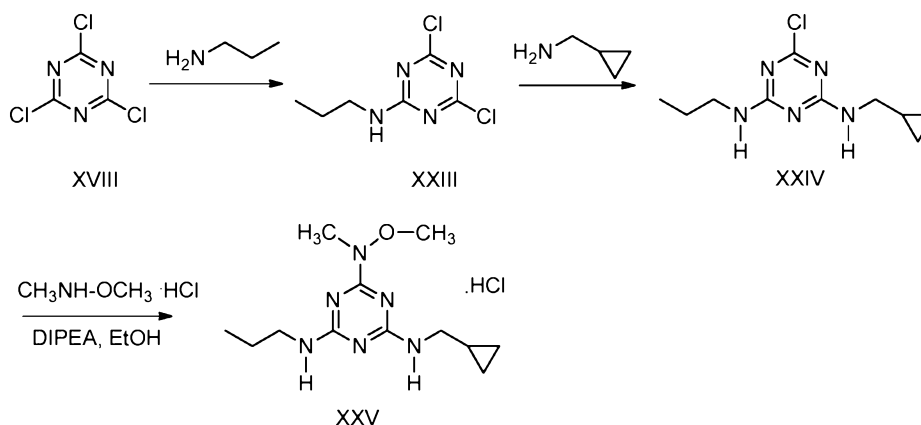
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N-(4,6-Bis-ethylamino-[1,3,5]triazin-2-yl)-*N*,*O*-dimethyl-hydroxylamine hydrochloride (XXII)

A mixture of 2-chloro-*N*-(4,6-bis-ethylamino)-[1,3,5]triazine (XXI) (4.03 g, 20 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (9.7 g, 100 mmol) and DIPEA (1.806 g, 140 mmol) in EtOH (200 mL) was heated at 100 °C for 16 h. After this time, the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (400 mL), washed with water (100 mL) and a brine solution (100 mL), then dried over Na₂SO₄ and concentrated. The crude product was purified by flash column chromatography (pet ether/ethyl acetate = 5/1 to 5/2) to yield 811 mg (18%) of the desired product. The isolated free amine (811 mg, 3.58 mmol) was dissolved in H₂O (10 mL) and 0.5 M HCl solution in H₂O (7.2 mL) was added. The resultant solution was lyophilized to yield the desired product, *N*-(4,6-bis-ethylamino-[1,3,5]triazin-2-yl)-*N*,*O*-dimethyl-hydroxylamine hydrochloride (XXII) as a white solid (938 mg). LCMS (ESI) *m/z* = 227 (*M*+H)⁺. ¹H NMR (500 MHz, DMSO): δ (ppm) 12.40-12.80 (br, 1H), 8.58-8.87 (m, 2H), 3.76-3.78 (m, 4H), 3.34-3.37 (m, 6H), 1.10-1.16 (m, 6H).

Example 3:

N-(4-Cyclopropylmethyl)-*N*-(6-*n*-propylamino) [1,3,5]triazin-2-yl)-*N*,*O*-dimethyl-hydroxylamine (XXV)



Scheme 10

2,4-Dichloro-N-(6-*n*-propylamino)-[1,3,5]triazine (XXIII)

2,4,6-Trichloro-1,3,5-triazine (XVIII) (20 g, 109 mmol) was dissolved in acetone (100 mL) and poured into ice-water (50 mL) to form a very fine

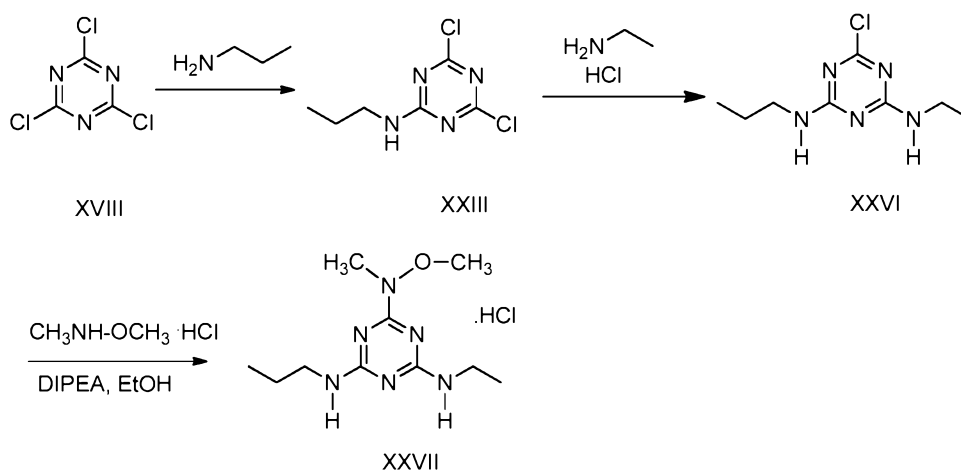
suspension. A solution of propan-1-amine (7.1 g, 120 mmol) in water (20 mL) was added and the temperature maintained at approximately 0 °C. To this mixture, 2N NaOH (60 mL, 120 mmol) was added in a dropwise manner to keep the temperature between -5 °C and 0 °C. The mixture was stirred at 0 °C for 60 min. The precipitate
5 was filtered off and washed with water (3 x 25 mL). After drying over calcium chloride under high vacuum, 2,4-dichloro-N-(6-*n*-propylamino)-[1,3,5]triazine (XXIII) was isolated as a white powder (18 g, 80% yield). LCMS (ESI) m/z = 208 (M+H)⁺.

10 *2-Chloro-N-(4-cyclopropylmethyl)-N-(6-n-propylamino) [1,3,5]triazine (XXIV)*
2,4-Dichloro-N-(6-*n*-propylamino)-[1,3,5]triazine (XXIII) (18 g, 87 mmol) was dissolved in acetone (100 mL) and poured into ice-water (50 mL) to form a very fine suspension. A solution of cyclopropylmethanamine (6.7 g, 95 mmol) in acetone (30 mL) was added and the temperature was maintained at approximately 0
15 °C. To this mixture, 2N NaOH (44 mL, 88 mmol) was added in a dropwise manner to keep the temperature between 0 °C and 5 °C. The mixture was stirred for 30 min at ambient temperature and for an additional 60 min at 50 °C. The precipitate was filtered off, washed with water (3 x 25 mL). After drying over anhydrous calcium chloride under high vacuum, 2-chloro-N-(4-cyclopropylmethyl)-N-(6-*n*-propylamino)
20 [1,3,5]triazine (XXIV) was isolated as a white powder (12 g, 57% yield). LCMS (ESI) m/z = 242 (M+H)⁺.

N-(4-Cyclopropylmethyl)-N-(6-n-propylamino) [1,3,5]triazin-2-yl)-N,O-dimethylhydroxylamine hydrochloride (XXV)

25 A mixture of 2-chloro-N-(4-cyclopropylmethyl)-N-(6-*n*-propylamino) [1,3,5]triazine (XXIV) (1.5 g, 6.2 mmol), N,O-dimethylhydroxylamine hydrochloride (3.0 g, 31.0 mmol) and DIPEA (6.5 g, 49.6 mmol) in EtOH (50 mL) was heated at 100 °C for 16 h, after the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (400 mL), washed with water (100 mL), then with a brine
30 solution (100 mL) and dried over Na₂SO₄. The crude was purified by flash column chromatography (pet ether/ethyl acetate = 5/1 to 5/2). The solvent was removed under reduced pressure to yield 500 mg (26%) of the desired product. The isolated free amine (500 mg, 1.88 mmol) was dissolved in H₂O (10 mL) and 0.5 M aqueous HCl solution (4.0 mL) was added. The resultant solution was subjected was subjected

Example 4:
N-(4-Ethylamino)-N-(6-*n*-propylamino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-
0 hydroxylamine (XXVII)



Scheme 11

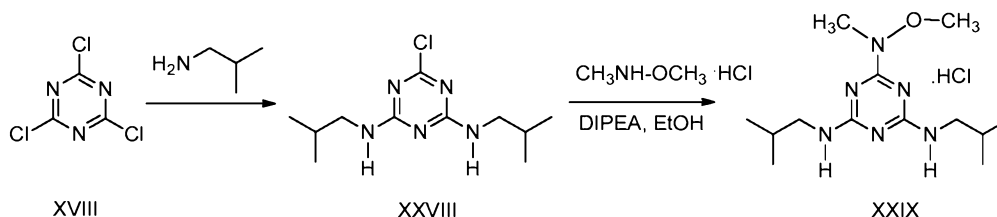
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2-Chloro-N-(4-ethylamino)-N-(6-n-propylamino)-[1,3,5]triazine (XXVI)

2,4-Dichloro-N-(6-n-propylamino)-[1,3,5]triazine (XXIII) (4.0 g, 19.5 mmol) was dissolved in acetone (40 mL) and poured into ice-water (40 mL) to form a very fine suspension. A solution of ethanamine hydrochloride (1.91 g, 23.4 mmol) in water (10 mL) was added and the temperature was maintained at approximately 0 °C. A solution of NaOH (2.34 g, 58.5 mmol) in water (10 mL) was added in a dropwise manner to keep the temperature between 0 °C and 5 °C. The mixture was then stirred 40 min at room temperature and concentrated. The precipitate was filtered off, washed with water (3 x 25 mL). After drying over calcium chloride under high vacuum, the desired product, 2-chloro-N-(4-ethylamino)-N-(6-n-propylamino)-[1,3,5]triazine (XXVI) was isolated as a white powder (3.89 g, 92% yield). LCMS (ESI) $m/z = 216$ (M+H)⁺.

N-(4-Ethylamino)-N-(6-n-propylamino) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (XXVII)

A mixture of 2-chloro-N-(4-ethylamino)-N-(6-n-propylamino)-[1,3,5]triazine (XXVI) (2 g, 9.3 mmol), N,O-dimethylhydroxylamine hydrochloride (4.5 g, 46.5 mmol) and DIPEA (8.4 g, 65.1 mmol) in EtOH (20 mL) was heated at 100 °C for 16 h, after which time the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (150 mL), washed with water (100 mL), washed with a brine solution (100 mL) and then dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (pet ether/ethyl acetate = 10/1 to 2/1) to yield the desired product (820 mg, 37%). The isolated free amine (820 mg, 3.42 mmol) was dissolved in H₂O (10 mL), and 0.5 M aqueous HCl solution (11 mL) was added. The resultant solution was subjected to lyophilization to yield the desired product, N-(4-ethylamino)-N-(6-n-propylamino) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (XXVII), as a colorless oil (944 mg). LCMS (ESI) $m/z = 241$ (M+H)⁺. ¹H NMR (500 MHz, DMSO): δ (ppm) 12.25-12.75 (br, 1H), 8.71-8.75 (m, 2H), 3.75-3.92 (m, 6H), 3.25-3.37 (m, 4H), 1.50-1.55 (m, 2H), 1.09-1.16 (m, 3H), 0.87-0.94 (m, 3H).

Example 5:N-(Bis-4,6-(2-methylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXIX)

5

Scheme 12*2-Chloro-N-(4, 6-bis-(2-methylpropylamino)-[1,3,5]triazine (XXVIII)*

2,4,6-Trichloro-1,3,5-triazine (XVIII) (5.0 g, 27 mmol) was dissolved in acetone (35 mL) and poured into ice-water (50 mL) to form a very fine suspension.

10 A solution of 2-methylpropan-1-amine (4.0 g, 54 mmol) in acetone (20 mL) was added and the temperature was maintained at approximately 0°C. To this mixture, 2 N NaOH (27 mL, 54 mmol) was added in a dropwise manner to keep the temperature between 0°C and 5°C. The mixture was stirred for 30 min at ambient temperature and for an additional 60 min at 50°C. The precipitate was filtered off, washed with water

15 (3 x 25 mL). After drying over calcium chloride under high vacuum, 2-chloro-N-(4, 6-bis-(2-methylpropylamino)-[1,3,5]triazine (XXVIII) was isolated as white powder (6.0 g, 87% yield). LCMS (ESI) $m/z = 258$ (M+H)⁺.

20 *N-(Bis-4,6-(2-methylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (XXIX)*

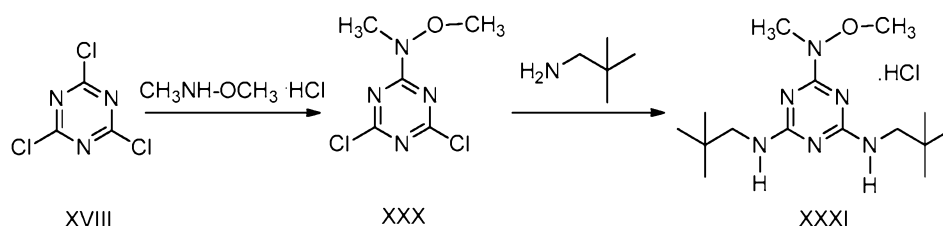
A mixture of 2-chloro-N-(4, 6-bis-(2-methylpropylamino)-[1,3,5]triazine (XXVIII) (2.57 g, 10 mmol), N,O-dimethylhydroxylamine hydrochloride (1.94 g, 20 mmol) and DIPEA (5.16 g, 40 mmol) in EtOH (100 mL) was heated at 100 °C for 16 h, after which time the solvent was removed under

25 reduced pressure. The residue was dissolved in EtOAc (200 mL), washed with water (2 x 100 mL), washed with a brine solution (100 mL) and then dried over Na₂SO₄. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (pet ether/ethyl acetate = 5/1) to yield the desired product (920 mg, 33%). The isolated free amine (920 mg, 3.3 mmol) was dissolved in H₂O

(10 mL) and 0.5 M aqueous HCl solution (6.6 mL) was added. The resultant solution was subjected to lyophilization to yield the desired product, N-(bis-4,6-(2-methylpropylamino))[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (XXIX) as a white solid (1.0 g). LCMS (ESI) $m/z = 283$ (M+H)⁺. ¹H NMR (500 MHz, DMSO): δ (ppm) 12.55-12.60 (br, 1H), 8.57-8.77 (br, 2H), 3.78 (s, 3H), 3.40-3.45 (m, 3H), 3.11-3.19 (m, 4H), 1.80-1.86 (m, 2H), 0.89-0.94 (m, 12H).

Example 6:

N-(Bis-4,6-(2,2-dimethylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (XXXI)



Scheme 13

N-(4,6-Dichloro[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXX)

2,4,6-Trichloro-1,3,5-triazine (XVIII) (30 g, 163 mmol) was dissolved in acetone (300 mL), and N,O-dimethylhydroxylamine hydrochloride (15.8 g, 163 mmol) and DIPEA (42 g, 326 mmol) were added and the mixture then stirred at 0°C for 1 h. The solution was concentrated and the residue was treated with EtOAc (750 mL), washed with water (100 mL), and the organic layer was dried with Na₂SO₄. The volatiles were removed in vacuo and the residue was purified by flash column chromatography (pet ether/ethyl acetate = 50/1 to 10/1) to yield the desired product, N-(4,6-dichloro[1,3,5] triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXX), as a white solid (25 g, 73% yield). LCMS (ESI) $m/z = 210$ (M+H)⁺.

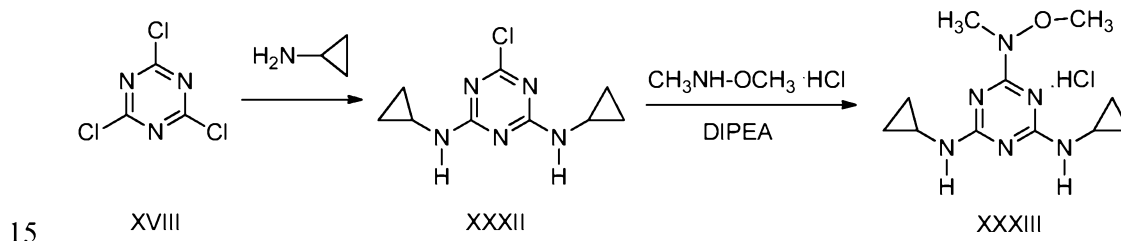
N-(Bis-4,6-(2,2-dimethylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXI)

A mixture of N-(4,6-dichloro[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXX) (1 g, 4.78 mmol), 2,2-dimethylpropan-1-amine (832.5 mg, 9.57 mmol) and DIPEA (1.85 g, 14.34 mmol) in EtOH (20 mL) was heated at 100 °C for 16 h, after which time the solvent was removed under reduced pressure. The

residue was dissolved in EtOAc (40 mL), washed with water (20 mL) and with a brine solution (20 mL), dried over Na₂SO₄, and then concentrated. The crude product was purified by flash column chromatography (pet ether/ethyl acetate = 20/1 to 5/1) to yield the desired product (1.4 g, 95%). The isolated free amine (1.4 g, 4.52 mmol) was dissolved in H₂O (10 mL) and 0.5 M HCl solution in H₂O (14.5 mL) was added, and the resultant solution was subjected to lyophilization to yield the desired product, N-(bis-4,6-(2,2-dimethylpropylamino))[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride, as a white solid (1.67 g). LCMS (ESI) m/z = 311 (M+H)⁺. ¹H NMR (500 MHz, DMSO): δ (ppm) 12.40-12.70 (br, 1H), 8.52-8.81 (m, 2H), 3.75-3.79 (m, 3H), 3.33-3.36 (m, 3H), 3.14-3.21 (m, 4H), 0.89-0.96 (m, 18H).

Example 7:

4,6-Bis-N-cyclopropylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (XXXIII)



Scheme 14

2-Chloro-N-(4, 6-bis-(cyclopropylamino)-[1,3,5]triazine (XXXII)

20 2,4,6-Trichloro-1,3,5-triazine (XVIII) (40 g, 217 mmol) was dissolved in 200 mL of acetone and poured into ice-water (250 mL) to form a very fine suspension. A solution of cyclopropanamine (24.8 g, 435 mmol) was added with stirring at 0°C. To this mixture, 2N NaOH (218 mL, 435 mmol) was added dropwise at a rate to keep the temperature between 0°C and 5°C. The resultant mixture was stirred for 30 min at ambient temperature and then for an additional 60 min at 50°C. The precipitate was filtered off, washed with water (3 × 100 mL). After drying over calcium chloride under high vacuum, chloro-N-(4, 6-bis-(cyclopropylamino)-[1,3,5]triazine (XXXII) was isolated as a white powder (46 g, 93% yield). LCMS (ESI) m/z = 226 (M+H)⁺.

30

4,6-Bis-N-cyclopropylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXIII)

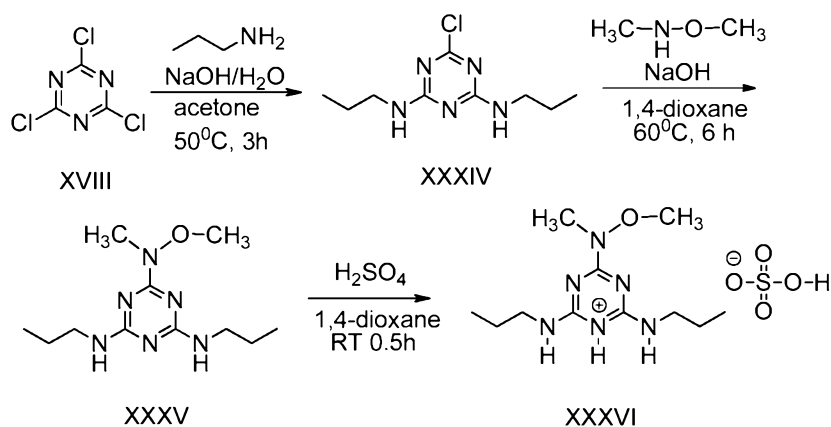
A mixture of chloro-N-(4, 6-bis-(cyclopropylamino)-[1,3,5]triazine (XXXII) (2.25 g, 10 mmol), N,O-dimethylhydroxylamine hydrochloride (1.94 g, 20 mmol) and DIPEA (5.16 g, 40 mmol) in EtOH (100 mL) was heated at 100 °C for 16 h, and the solvent was then removed under reduced pressure. The residue was dissolved in EtOAc (200 mL), washed with water (2 × 100 mL) and brine (100 mL) then dried over Na₂SO₄. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (pet ether/ethyl acetate = 3/1) to yield 1.0 g (40%) of the desired product. The isolated free amine (1.0 g, 4.0 mmol) was dissolved in H₂O (10 mL) and 0.5 M aqueous HCl solution (8 mL) and then the solution was lyophilized to yield N-(4,6-bis-cyclopropylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (XXXIII) as a white solid (1.05 g). LCMS (ESI) m/z = 251 (M+H)⁺. ¹H NMR (500 MHz, DMSO): δ (ppm) 12.00-12.80 (br, 1H), 8.70-9.50 (br, 2H), 3.76 (s, 3H), 3.28-3.38 (m, 3H), 2.69-2.89 (m, 2H), 0.59-0.81 (m, 8H).

Example 8A:

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV)

Example 9A:

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI)



Scheme 15A

25

2-Chloro-N-(4,6-bis-(n-propylamino)-[1,3,5]triazine (XXXIV)

A 2 M NaOH solution (82 mL, 162.68 mmol) was added in a dropwise manner to a suspension of 2,4,6-trichloro-1,3,5-triazine (XVIII) (15.00 g, 81.34 mmol) and *n*-propylamine (13.4 mL, 162.68 mmol) in acetone (300 mL) and water (15 mL) at 0°C. The reaction mixture was heated at 50 °C for 3 h and then cooled.

- 5 Water (100 mL) was added to the reaction mixture; the resultant precipitate was filtered, washed with water, ethyl ether and dried to yield 2-chloro-N-(4, 6-bis-(*n*-propylamino)-[1,3,5]triazine (XXXIV) (15.88 g, 85% yield).

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-*N*,*O*-dimethyl-hydroxylamine (XXXV)

- 10 A mixture of 2-chloro-N-(4, 6-bis-(*n*-propylamino)-[1,3,5]triazine (XXXIV) (10.00 g, 43.53 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (8.49 g, 87.06 mmol) and NaOH (3.13 g, 78.35 mmol) in 1,4-dioxane (120 mL) and water (30 mL) was heated at 60 °C for 6 h, after which the volatiles were removed under reduced pressure. Saturated NaHCO₃ solution (500 mL) was added to the residue and
15 the mixture was extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with water (300 mL), then with a brine solution (300 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the resultant residue was filtered through silica gel using eluent CH₂Cl₂/EtOH (9/1 v/v) to yield *N*-(4,6-bis-*n*-propylamino [1,3,5]triazine-2-yl)-*N*,*O*-dimethyl-hydroxylamine (XXXV) (9.96 g,
20 90% yield).

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-*N*,*O*-dimethyl-hydroxylamine hydrogen sulfate (XXXVI)

- Concentrated (95%) H₂SO₄ (0.72 mL, 12.74 mmol) was added in a
25 dropwise manner to a solution of *N*-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-*N*,*O*-dimethyl-hydroxylamine (XXXV, 3.24 g, 12.74 mmol) in 1,4-dioxane (100 mL) at 0°C. The mixture was stirred for 0.5 h at room temperature, volatiles were removed under reduced pressure. The residue was co-evaporated with dry toluene (3 x 25 mL). The resulting white residue was crystallized from ethanol/ethyl ether to yield *N*-(4,6-
30 bis-*n*-propylamino-[1,3,5]triazin-2-yl)-*N*,*O*-dimethyl-hydroxylamine, hydrogen sulfate (XXXVI, 3.86g, 86% yield) as a white solid. ¹H NMR (400 MHz, DMSO): δ (ppm) 12.0-11.2 (1H, br s), 8.7-8.3 (0.7 H, br s), 8.10 (0.3H, br s), 7.8-7.3 (1H, m),

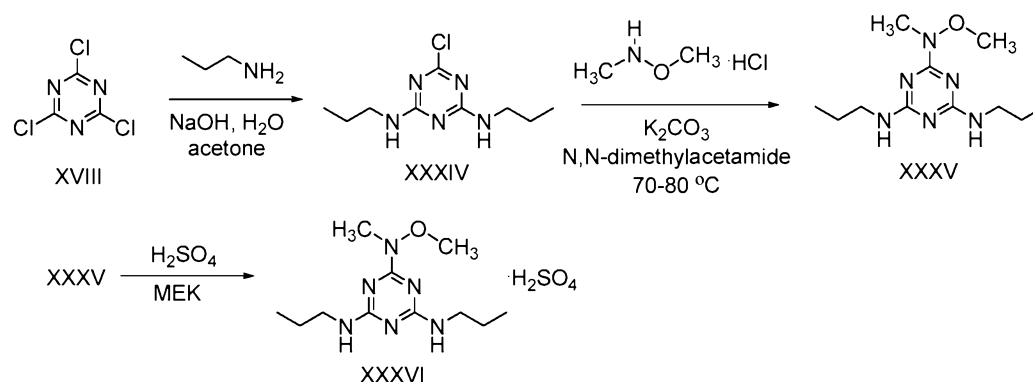
3.78 (3H, s), 3.40-3.20 (7H, m), 1.61-1.45 (4H, m), 0.93-0.84 (6H, m). ESI-MS (m/z) 255 [M+H]⁺; melting point: 134-135 °C.

Example 8B:

5 N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV)

Example 9B:

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine
hydrogen sulfate (XXXVI)



10

Scheme 15B

Stage 1: 2-Chloro-N-(4,6-bis-(*n*-propylamino)-[1,3,5]triazine (XXXIV)

Summary: Di-chloro displacement by 2 equivalents of *n*-propylamine.

In one embodiment, two or more equivalence of *n*-propylamine produced only the
15 bis-propylamine derivative of the starting material. The reaction progress was
monitored by HPLC and the desired intermediate (2-chloro-4,6-bis-*n*-propylamino-s-
triazine) was precipitated. In-process QC Tests were performed.

A suitable glass reactor vessel equipped with a mechanical stirrer,
thermocouple, condenser, addition funnel and a temperature control mantle was
20 charged with 8 L of acetone followed by 1 kg (5.42 moles) of cyanuric chloride. The
stirring mixture was pre-cooled to 15 °C and *n*-propylamine (at ambient temperature)
was added slowly via addition funnel, to maintain the temperature below 45°C. A 2M
NaOH solution was prepared and was added to the mixture at a rate to maintain the
temperature below 45°C. The pH of the mixture was acidic (approximately pH = 4)
25 and 6N NaOH was added to adjust the pH to 8-9. The mixture was stirred at 40-50°C
for 0.5 h and the reaction was monitored for completion by IPC HPLC analysis. The

reaction was deemed complete when <2% of cyanuric chloride was detected.

Analysis was repeated every hour until reaction was complete.

After reaction was complete, WFI (sterile water) was added slowly to maintain temperature below 50°C. The resulting suspension was allowed to cool to room temperature while stirring overnight. The solids were filtered through a polypropylene filter cloth and washed with acetone/water (1:2) followed by 1.5 L of MTBE. The solids were dried on the filter (assisted by vacuum) then placed in a vacuum oven (45±5 °C, > 29" Hg) for a minimum of 6 h to give <0.5% in change in weight loss. A sample was collected for analytical testing (QC HPLC analysis and Karl Fisher analysis); 2 g was collected for QA retain. The product produced in Stage 1 was a white solid. This powder was transferred from drying pans to poly bag with nylon tie, double bagged and placed into fiber drum; label and submit to QA for quarantine storage.

15 Stage 2, Step 1: N-(4,6-Bis-n-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV)

Summary: Chloro displacement by 1 equivalent of N-methoxymethylamine. The reaction progress was monitored by HPLC and precipitation of desired product free base was accomplished by adding water and cooling. In-process QC Tests were pre-formed. The free base was converted to the corresponding sulfate salt with crystallization and the final product was subjected to vacuum oven drying. In-process QC Tests were performed as well as finished product QC testing.

A suitable round-bottom flask equipped with a mechanical stirrer, thermocouple, condenser and a heating mantle was charged with 6 L of N,N-dimethylacetamide (DMA) followed by 1 kg (4.35 moles) of 6-chloro-N,N-dipropyl-[1,3,5]-triazine-2,4-diamine (Stage 1 Product). Added to this stirring mixture at room temperature was K₂CO₃ (1.2 kg, 6.53 moles, 2 eq.), with rinsing with a small quantity of additional DMA. To this, was added N,O-dimethylhydroxylamine hydrochloride (0.637 kg, 8.71 moles, 1.5 eq.) in portions over ~5-10 minutes to reduce foaming (and while maintaining the temperature below 60°C) with rinsing using a small quantity of additional DMA. The mixture was heated to 75-80°C and stir for a minimum of 0.5 hours. Once at 75-80°C, the reaction was monitored for completion by HPLC. The mixture was cooled to below 65°C and water (12 L) was added. The resulting

suspension was allowed to cool to room temperature while stirring overnight (18 h). The resultant solids were filtered and washed with 1.2 L of water. The filter cake to air-dry one hour and a sample for OVI amine GC analysis was obtained. The remaining solids were vacuum oven dried (45°C, > 29" Hg) for a minimum of 6 hours
 5 (NMT 1% weight change). The desired product (free base (XXXV)) was a dense white solid. An IPC sample for testing was obtained.

Crystalline N-(4,6-Bis-n-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine free base (XXXV)

A solution of (XXXV) free base in methylene chloride was rapidly
 10 evaporated to dryness. The resulting solid was dried under vacuum at ca. 25°C for ca. 45 minutes (XXXV freebase Form A). DSC: Sharp endotherm at ca. 95.2°C. XRPD: Figure 22.

Stage 2, Step 2: Salt Formation and Crystallization of N-(4,6-Bis-n-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI)

15 Methyl ethyl ketone (20L) was added to 2,800 g (12.2 moles) of substrate free base (XXXV). The mixture was stirred and heated to 40°C then polish filtered into a 72-L reactor through a medium porosity sintered glass funnel to yield a clear solution and a fluffy white residue (12 g, 0.43% of the free base weight). The mixture was warmed to 45°C and concentrated H₂SO₄ (12.8 moles, 1.05 eq. based on
 20 pre-filtered weight) was added slowly over 1h via addition funnel. The mixture was allowed to stir overnight (18 h) while cooling (A solid precipitate was observed to begin forming at approximately 36°C; final temp = 27°C).

The mixture was further cooled to 15°C, stirred 0.5h and filtered. The solid product cake was washed with methyl ethyl ketone (6L), air dried on the
 25 Büchner funnel (vacuum assisted) for 4 h, then placed in a vacuum oven (>29" Hg, 50-55°C) and dried for at least 6 h to give 3,252g (84%) of N-(4,6-Bis-n-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.88 (quin., 6 H), 1.41-1.63 (m, 4 H), 3.16-3.40 (m, 7 H), 3.69-3.83 (m, 3 H), 7.50-8.56 (m, 2 H). In
 30 Process Purity (HPLC (AUC @ 210nm) = 99.81%. Filter residue: ¹H NMR (400 MHz, methanol-*d*₄) 3.27-3.35 (m), 1.55-1.65 (q) 0.90-0.95 (t). MS m/z: 212 [M+H], consistent with data N-(4,6-bis(propylamino)-1,3,5-triazin-2-ol (CLXXVIII) (c.f.,

Comparative Example 1). The isolated title compound contained no detectable (CLXXVIII).

Stage 1:

- 5 IPC Test 1: Temperature Chart Recording during additions -

Maintain temperature control specified in process steps

IPC Test 2: IPC HPLC analysis -

Reaction is complete when <2% of cyanuric chloride is detected.

Repeat analysis every hour until reaction is complete.

- 10 Contact supervisor if reaction is not complete after third sample.

Stage 1 Product QC testing:

QC HPLC analysis -

Record results of assay of cyanuric chloride and 2-chloro-4,6-bis-*n*-propylamino-s-triazine

- 15 Karl Fisher -

Record results

Stage 2:

Step 1: Reaction:

- 20 IPC Test 1: Temperature Chart Recording during additions -

Maintain temperature control specified in process steps

IPC Test 2: IPC HPLC analysis -

Reaction is complete when <2% of 2-chloro-4,6-bis-*n*-propylamino-s-triazine is detected.

- 25 Repeat analysis every hour until reaction is complete.

Contact supervisor if reaction is not complete after third sample.

IPC Test 3: Residual amine analysis (by GC) -

n-Propylamine and N,O-dimethylhydroxylamine levels NMT 0.1%

IPC Test 4: Weight Change during drying -

- 30 NMT 1%

IPC Test 5: IPC HPLC analysis -

Purity by HPLC (AUC) record results

Step 2: Salt Formation and Crystallization

IPC Test 1: Temperature Chart Recording during concentrated sulfuric acid addition -

Maintain temperature control specified in process step

IPC Test 2: OVI of MEK and DMAc by GC -

NMT 800ppm each

IPC Test 4: Weight Change during drying -

5 NMT 1%

Proton Nuclear Magnetic Resonance (NMR) Spectroscopy

¹H NMR data of N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) was obtained as a solution in DMSO-d₆ at 400 MHz and is presented in Figure 10 and shift assignments are presented in Table 1.

Table 1:

¹H Chemical shift assignments for (XXXVI) in DMSO-d₆ at 25°C

Resonance Peak	$\delta^1\text{H}$ (ppm)	Assignment
1	0.88	13, 17
2	1.53	12, 16
3	3.30	11, 15
4	3.35	18
5	3.77	9
6	[7.42, 8.70]	10, 14

15 Carbon-13 NMR Spectroscopy

¹³C NMR data of N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) was obtained as solutions in DMSO-d₆ at 100 MHz and is presented in Figure 11 and shift assignments are presented in Table 2.

Table 2:

¹³C Chemical shift assignments for (XXXVI) in DMSO-d₆ at 25°C.

Resonance peak	$\delta^{13}\text{C}$ (ppm)	Assignment
1	11.25	13, 17
2	21.88	12, 16
3	34.08	18
4	42.24	11, 15
5	61.86	9
6	154.63	2
7	155.79	4, 6

Fourier Transform Infrared (FTIR) Spectroscopy

The FTIR spectrum of N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) is presented in Table 3 and Figure 12.

5

Table 3:

FTIR spectrum of (XXXVI)

Wavenumber (cm ⁻¹)	Assignment
3284	N-H stretch
2850-2960	C-H stretch
1615-1700	C=N bend
1536-1656	N-H bend
1020-1340	C-N stretch

High and Low Resolution Mass Spectrometry

The mass obtained from Liquid Chromatography-Mass Spectrometry (LCMS) was 254 amu, which agrees with the theoretical mass of N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI). High-resolution results obtained through direct injection are presented in Table 4.

15

Table 4:

Mass spec results for (XXXVI)

Calculated Molecular Weight	Theoretical Exact Mass	Formula
254.1863	254.1855	C ₁₁ H ₂₂ N ₆ O

Chromatographic Purity

The HPLC chromatographic purity of the RS was determined to be 100.0% by area, with no related substances detected.

20

Water by Determination

The water content was determined to be 0.04% by Karl Fischer titration.

25 Elemental Analysis

Elemental analysis of N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) was obtained and is presented in Table 5.

Table 5:

Elemental analysis results for (XXXVI)

Element	Theoretical (%)	Result (%)
C	37.49	37.59
H	6.86	6.95
N	23.85	23.86
S	9.10	9.08

Thermal Analysis by Differential Scanning Calorimetry (DSC)

- 5 N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) was analyzed from 25 °C to 250 °C, at a rate of 10 °C per minute as per cUSP <891> / EP 2.2.34 and was found to have endotherms at 90.19 °C, 126.38 °C, and 138.30°C Figure 13.

10 X-ray Powder Diffraction

XRPD diffraction pattern of N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) was obtained and is consistent with Form A; presented in Figure 14.

15 Counterion Content

N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) was found to contain 27.13% sulfate content by titration.

20 pH of Aqueous Solution

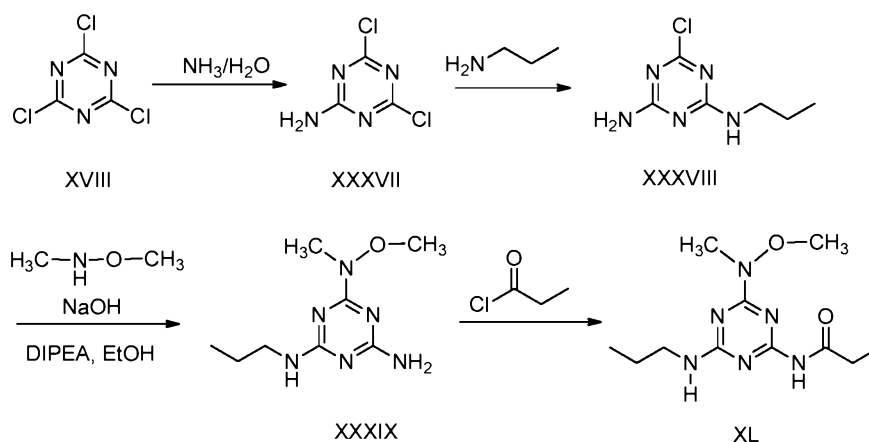
A 1% aqueous solution of N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) yielded a pH of 1.89.

Physical Description

- 25 N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) was determined to be a white crystalline solid.

Example 10:

N-(4-(Methoxy(methyl)amino)-6-(propylamino)-1,3,5-triazin-2-yl)propionamide
(XL)



Scheme 16

5

6-Amino-2,4-dichloro-[1,3,5]triazine (XXXVII)

2,4,6-Trichloro-1,3,5-triazine (XVIII) (10.0 g, 55 mmol) was dissolved in acetone (80 mL) and poured into ice-water (80 mL) to form a very fine suspension. To this mixture, 1 N ammonium hydroxide solution (108 mL, 109.4 mmol) was added at 0°C. The reaction was stirred for 30 min at ambient temperature and for additional 60 min at 25 °C. The precipitate was filtered off, washed with water (3 x 25 mL). After drying over calcium chloride under high vacuum, 6-amino-2,4-dichloro-[1,3,5]triazine (XXXVII) was isolated as white powder (7.4 g, 82% yield). LCMS (ESI) $m/z = 165$ (M+H)⁺.

15

6-Amino-2-chloro-4-n-propylamino-[1,3,5]triazine (XXXVIII)

6-Amino-2,4-dichloro-[1,3,5]triazine (XXXVII) (30.0 g, 187 mmol) was dissolved in acetone (100 mL) and poured into ice-water (100 mL) to form a very fine suspension. To this mixture, a solution of propan-1-amine (11.0 g, 187 mmol) in acetone (20 mL) was added at 0°C. To this reaction, 2 N NaOH (94 mL, 187 mmol) was added dropwise at a rate to keep the temperature between 0°C and 5°C. The mixture was stirred for 30 min at ambient temperature and for an additional 60 min at 50°C. The mixture was concentrated and then the precipitate was filtered off and washed with water (3 x 100 mL). After drying over calcium chloride under high vacuum, 6-amino-2-chloro-4-*n*-propylamino-[1,3,5]triazine (XXXVIII) was isolated as a white powder (35 g, 100% yield). LCMS (ESI) $m/z = 188$ (M+H)⁺.

N-(6-Amino-4-*n*-propylamino-[1,3,5]triazin-2-yl)-*N*,*O*-dimethyl-hydroxylamine (XXXIX)

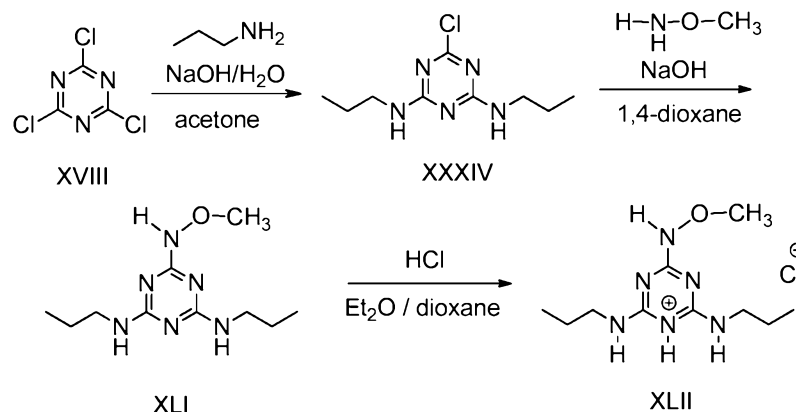
A mixture of 6-amino-2-chloro-4-*n*-propylamino-[1,3,5]triazine (XXXVIII) (5 g, 26.65 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (13 g, 133.24 mmol) and DIPEA (27.5 g, 213.2 mmol) in EtOH (100 mL) was heated at 100 °C for 16 h, after which time the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (400 mL), which was washed with water (200 mL) and then with a brine solution (200 mL) and finally dried over Na₂SO₄. The solvent was removed under reduced pressure to yield *N*-(6-amino-4-*n*-propylamino-[1,3,5]triazin-2-yl)-*N*,*O*-dimethyl-hydroxylamine (XXXIX) as a white solid (5 g, 89% yield). LCMS (ESI) *m/z* = 213 (M+H)⁺.

N-(4-(Methoxy(methyl)amino)-6-(propylamino)-1,3,5-triazin-2-yl)propionamide (XL)

N-(6-amino-4-*n*-propylamino-[1,3,5]triazin-2-yl)-*N*,*O*-dimethyl-hydroxylamine (XXXIX) (5 g, 23.58 mmol) was dissolved in THF (50 mL). Propionyl chloride (3.25 g, 35.38 mmol) and DIPEA (5.47 g, 42.44 mmol) were added at 0 °C. The resultant mixture was stirred at ambient temperature for 10 min, then stirred at 70 °C for 16 h, after which time the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (250 mL), and this extract was washed with water (80 mL) and then with a brine solution (80 mL), and lastly dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (pet ether/ethyl acetate = 5/1 to 2/1) to yield 930 mg (15%) of the desired product. The isolated free amine (930 mg, 3.47 mmol) was dissolved in H₂O (10 mL) and 0.5 M HCl solution in H₂O (10.4 mL) and then the solution was lyophilized to yield *N*-(4-(methoxy(methyl)amino)-6-(*n*-propylamino)-1,3,5-triazin-2-yl)propionamide (XL) as a colorless oil (1.06 g). LCMS: (ESI) *m/z* = 269 (M+H)⁺. ¹H NMR (500 MHz, DMSO): δ (ppm) 12.23 (s, 1H), 8.25-9.45 (m, 2H), 3.76-3.84 (m, 3H), 3.30-3.44 (m, 5H), 2.55-2.56 (m, 1H), 2.21-2.22 (m, 1H), 1.53-1.58 (m, 2H), 0.88-1.08 (m, 6H).

Example 11:

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-*O*-methyl-hydroxylamine (XLI)

Example 12:N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-methyl-hydroxylamine hydrochloride (XLII)

5

Scheme 17*2-Chloro-N-(4, 6-bis-(n-propylamino)-[1,3,5]triazine (XXXIV)*

A 2 M NaOH solution (163 mL, 325.36 mmol) was added in a dropwise manner to a suspension of 2,4,6-trichloro-1,3,5-triazine (XVIII) (30.0 g, 162.68 mmol) and *n*-propylamine (26.8 mL, 325.36 mmol) in acetone (600 mL) and water (30 mL) at 0°C (water – ice/NaCl bath). The ice bath was removed and the reaction mixture was heated at 50 °C for 3 h, then cooled. Water (200 mL) was added to the reaction mixture; the precipitate was filtered, washed with water (200 mL) and dried over P₂O₅ at 40°C for 20 h to yield 2-chloro-N-(4, 6-bis-(*n*-propylamino)-[1,3,5]triazine (XXXIV, 33.6 g, 90% yield). 400 MHz ¹H NMR (DMSO-d₆, ppm) 7.80 (0.85H, t, J=5.5 Hz), 7.76-7.66 (1H, m), 7.49 (0.15H, t, J=5.5 Hz), 3.22-3.11 (4H, m), 1.55-1.42 (4H, m), 0.88-0.82 (6H, m). ESI-MS (m/z): 230, 232 [M+H]⁺.

N-(4,6-Bis-n-propylamino-[1,3,5]triazin-2-yl)-O-methyl-hydroxylamine (XLI)

A mixture of 6-chloro-N,N'-dipropyl-[1,3,5]triazine-2,4-diamine (XXXIV) (2.30 g, 10.01 mmol), O-methyl-hydroxylamine hydrochloride (1.67 g, 20.02 mmol) and NaOH (0.72 g, 18.00 mmol) in 1,4-dioxane (30 mL) and water (6 mL) was heated at 60 °C for 3 h. After this time, NaOH (0.72 g, 18.00 mmol) was added and the reaction mixture was heated for another 3 h. The volatiles were removed under reduced pressure. Saturated NaHCO₃ solution (100 mL) was added to

the residue, the mixture was extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using gradient elution from CH₂Cl₂/EtOH (99:1) to CH₂Cl₂/EtOH (95:5) to yield 2.17 g (90%) of N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-methyl-hydroxylamine (XLI). ESI-MS (m/z): 241 [M+H]⁺

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-methyl-hydroxylamine hydrochloride (XLII)

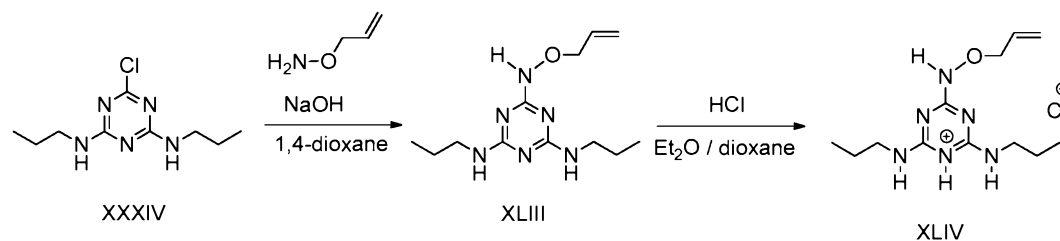
A 2M HCl /ethyl ether (4.5 mL, 9.00 mmol) was added to the solution N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-methyl-hydroxylamine (XLI) (2.17 g, 9.03 mmol) in 1,4-dioxane (5 mL) at 0°C. The mixture was stirred for 0.5 h at 0°C, volatiles were removed under reduced pressure to yield N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-methyl-hydroxylamine hydrochloride (XLII) in quantitative yield. 400 MHz ¹H NMR (DMSO-d₆, ppm) 12.5-11.5 (2H, br s), 8.49 (1H, br s), 8.34 (1H, br s), 3.71 (3H, s), 3.34-3.16 (4H, m), 1.59-1.46 (4H, m), 0.94-0.83 (6H, m). ESI-MS (m/z) 241 [M+H]⁺.

Example 13:

O-Allyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine (XLIII)

Example 14:

O-Allyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine hydrochloride salt (XLIV)



Scheme 18

O-Allyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine

A mixture of 2-chloro-N-(4,6-bis-*n*-propylamino)-[1,3,5]triazine (XXXIV) (2.00 g, 8.71 mmol), O-allyl-hydroxylamine hydrochloride (1.91 g, 17.42

mmol) and NaOH (0.70 g, 17.42 mmol) in 1,4-dioxane (25 mL) and water (5 mL) was heated at 60 °C for 4 h. The volatiles were removed under reduced pressure.

Saturated NaHCO₃ solution (100 mL) was added to the residue and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using gradient elution from CH₂Cl₂/EtOH (99:1) to CH₂Cl₂/EtOH (95:5) to yield O-allyl-N-(4,6-bis-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine (XLIII, 2.05 g, 88% yield). ESI-MS (m/z) 267 [M+H]⁺.

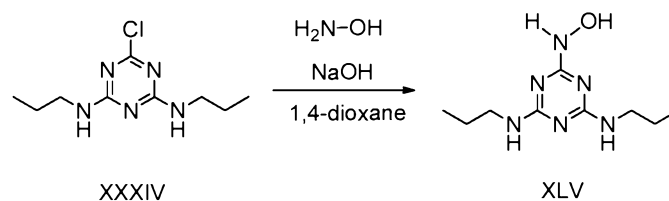
10

*O-Allyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine hydrochloride*

O-Allyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine hydrochloride (XLIV) was prepared from O-allyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine (XLIII) and 2M HCl /ethyl ether as described in Example 12. 400 MHz ¹H NMR (DMSO-d₆, ppm) 11.7-10.0 (1H, m), 7.9-7.1 (2H, m), 6.09-5.92 (1H, m), 5.39-5.18 (2H, m), 4.35 (2H, d, J=6.0 Hz), 3.28-3.11 (4H, m), 1.56-1.42 (4H, m), 0.91-0.81 (6H, m). ESI-MS (m/z): 267 [M+H]⁺. MP: 130-132°C.

20 Example 15:

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine (XLV)



Scheme 19

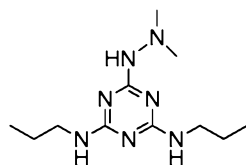
25 N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine (XLV) was prepared from 2-chloro-N-(4,6-bis-*n*-propylamino)-[1,3,5]triazine (XXXIV) and hydroxylamine hydrochloride as described in Example 13 (99% yield). 400 MHz ¹H NMR (DMSO-d₆, ppm) 9.0-8.6 (1H, br s), 8.39-8.14 (1H, s), 6.89-6.55 (2H, m), 3.23-3.06 (4H, m), 1.54-1.40 (4H, m), 0.84 (6H, t, J=7.4 Hz). ESI-MS (m/z): 227 [M+H]⁺. MP: 138-141°C.

30

Example 16N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N',N'-dimethylhydrazine (XLVI)

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N',N'-

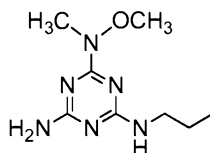
- 5 dimethylhydrazine (XLVI) may be prepared from 2-chloro-N-(4, 6-bis-(*n*-propylamino)-[1,3,5]triazine (XXXIV) and N,N-dimethylhydrazine as described in Example 19.



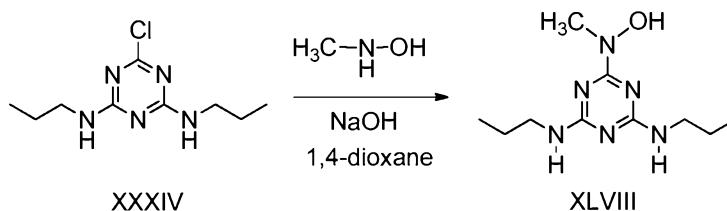
XLVI

Scheme 20Example 17

- 10 6-(Methoxy(methyl)amino)-N2-propyl-1,3,5-triazine-2,4-diamine (XLVII)

Scheme 21

- 15 6-(Methoxy(methyl)amino)-N2-propyl-1,3,5-triazine-2,4-diamine (XLVII) may be prepared from 6-amino-2-chloro-4-*n*-propylamino-[1,3,5]triazine (XXXVIII) and N,O-dimethylhydroxylamine as described in Example 10.

Example 18:N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine (XLVIII)

XXXIV

XLVIII

20

Scheme 22

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine (XLVIII) was prepared from 2-chloro-N-(4, 6-bis-(*n*-propylamino)-[1,3,5]triazine (XXXIV) and N-methyl-hydroxylamine hydrochloride as described in

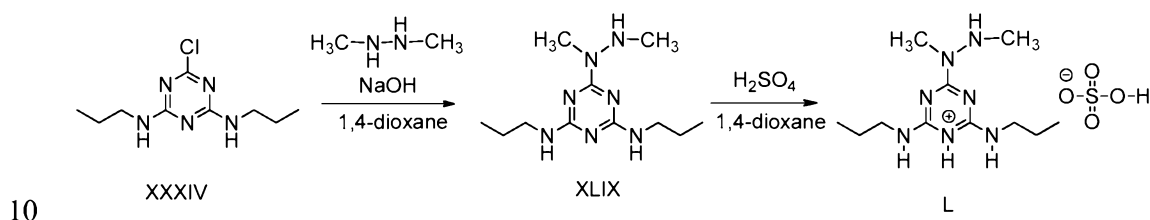
Example 13 (90% yield). 400 MHz ^1H NMR (DMSO- d_6 , ppm) 8.93 (1H, s), 6.92-6.43 (2H, m), 3.23-3.07 (7H, m), 1.55-1.38 (4H, m), 0.84 (6H, t, $J=7.4$ Hz). ESI-MS (m/z) 241 $[\text{M}+\text{H}]^+$.

5 Example 19:

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,N'-dimethyl-hydrazine (XLIX)

Example 20:

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,N'-dimethyl-hydrazine hydrogen sulfate (L)



Scheme 23

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-*N,N'*-dimethyl-hydrazine (XLIX)

15 A mixture of 2-chloro-*N*-(4,6-bis-(*n*-propylamino)-[1,3,5]triazine (XXXIV) (2.50 g, 10.88 mmol), *N,N'*-dimethyl-hydrazine dihydrochloride (2.89 g, 21.76 mmol) and NaOH (2.18 g, 54.40 mmol) in 1,4-dioxane (40 mL) and water (20 mL) was heated at 60 °C for 18 h. The volatiles were removed under reduced pressure. Saturated NaHCO_3 solution (100 mL) was added to the residue, the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with water (75 mL), brine (75 mL) and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using gradient elution ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ (99:1) to $\text{CH}_2\text{Cl}_2/\text{EtOH}$ (95:5)) to yield *N*-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-*N,N'*-dimethyl-hydrazine (1.17 g, 42%). 200 MHz ^1H NMR (DMSO- d_6 , ppm): 6.81-6.44 (2H, m), 5.31 (1H, br s), 3.24-3.08 (4H, m), 3.05 (3H, s), 2.47-2.40 (3H, m), 1.57-1.37 (4H, m), 0.84 (6H, t, $J=7.4$ Hz). ESI-MS (m/z): 254 $[\text{M}+\text{H}]^+$.

25

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-*N,N'*-dimethyl-hydrazine hydrogen sulfate (L)

30

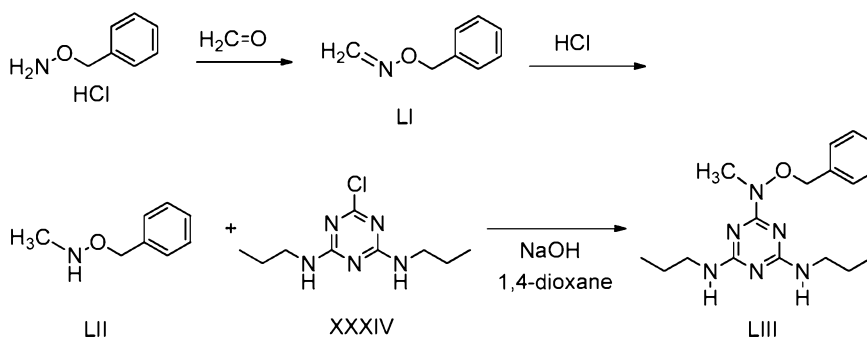
95% H₂SO₄ (0.26 mL, 4.62 mmol) was added dropwise to the solution of 6-(N,N'-dimethyl-hydrazino)-N,N'-dipropyl-[1,3,5]triazine-2,4-diamine (XLIX) (1.17 g, 4.62 mmol) in 1,4-dioxane (10 mL) at 0°C. The mixture was stirred for 0.5 h at room temperature; volatiles were removed under reduced pressure. The residue was co-evaporated with dry toluene (3 x 25 mL) to yield N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,N'-dimethyl-hydrazine hydrogen sulfate (L) in quantitative yield. 400 MHz ¹H NMR (DMSO-d₆, ppm) 8.48-8.32 (1H, m), 7.9-7.7 (0.5H, br s), 7.70-7.61 (0.5H, m), 3.34-3.20 (4H, m), 3.21 (1.5H, s), 3.17 (1.5H, s), 2.52 (1.5H, s), 2.51 (1.5H, s, overlapped with DMSO), 1.59-1.46 (4H, m), 0.93-0.82 (6H, m). ESI-MS (m/z): 254 [M+H]⁺.

Example 21:

O-Benzyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine (LIII)

Example 22:

O-Benzyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine hydrogen sulfate salt (LIV)



Scheme 24

20

Formaldehyde O-benzyl-oxime (LI)

A NaOH (1.25 g, 31.32 mmol) solution in water (6 mL) was added to the mixture of O-benzyl-hydroxylamine hydrochloride (5.00 g, 31.32 mmol) and formaldehyde (~37 wt. % in H₂O) (2.3 mL, 31.32 mmol) in toluene (40 mL). The reaction mixture was stirred at room temperature for 1 h. After this time, the organic phase was separated and the water phase was extracted with dichloromethane (3 x 30 mL). The combined organic phases were dried over Na₂SO₄, and concentrated *in vacuo* to yield formaldehyde O-benzyl-oxime (LI, 4.15 g, 98%). 400 MHz ¹H NMR

(CDCl₃, ppm) 7.40-7.29 (5H, m), 7.09 (1H, d, J=8.2 Hz), 6.47 (1H, d, J=8.2 Hz), 5.14 (2H, s).

O-Benzyl-N-methyl-hydroxylamine (LII)

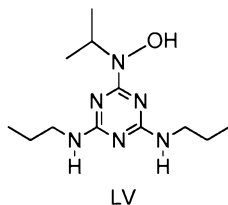
5 A 1M HCl/EtOH solution (50 mL) was added dropwise to the solution of formaldehyde O-benzyl-oxime (3.85 g, 28.48 mmol) in EtOH at 0 °C. The mixture was stirred at room temperature for 1 hour, volatiles were removed *in vacuo*. The residue was dissolved in dichloromethane (100 mL), washed with saturated NaHCO₃ solution (75 mL), water (75 mL), and dried over Na₂SO₄. The product was purified
10 by flash column chromatography using gradient elution from petroleum ether/EtOAc (9:1) to petroleum ether/EtOAc (7:1) to yield O-benzyl-N-methyl-hydroxylamine (1.72 g, 44%). 200 MHz ¹H NMR (CDCl₃, ppm) 7.40-7.27 (5H, m), 5.53 (1H, br s), 4.71 (2H, s), 2.73 (3H, s).

15 *O-Benzyl-N-(4,6-bis-n-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine (LIII)*

2-Chloro-N-(4, 6-bis-(n-propylamino)-[1,3,5]triazine (XXXIV) and O-benzyl-N-methyl-hydroxylamine (LII) were reacted as described in Example 13 to yield O-benzyl-N-(4,6-bis-n-propylamino-[1,3,5]triazin-2-yl)-N-methyl-
20 hydroxylamine (LIII) (29% yield). 200 MHz ¹H NMR (DMSO-d₆, ppm) 7.52-7.28 (5H, m), 7.07-6.67 (2H, m), 4.93 (2H, s), 3.26-3.03 (7H, m), 1.58-1.39 (4H, m), 0.85 (6H, t, J=7.2 Hz). ESI-MS (m/z): 331 [M+H]⁺.

25 *O-Benzyl-N-(4,6-bis-n-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine hydrogen sulfate (LIV)*

O-Benzyl-N-(4,6-bis-n-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine (LIII) was reacted with 95% H₂SO₄ as described in Example 20 to yield O-benzyl-N-(4,6-bis-n-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine hydrogen sulfate (LIV) in quantitative yield. 400 MHz ¹H NMR
30 (DMSO-d₆, ppm) 12.0-10.9 (1H, br s), 8.7-8.3 (1H, br s), 7.56-7.46 (2H, m), 7.46-7.37 (2.5H, m), 7.36-7.30 (0.5H, m), 5.07-4.95 (2H, m), 3.44-3.16 (7H, m), 1.61-1.45 (4H, m), 0.94-0.82 (6H, m). ESI-MS (m/z): 331 [M+H]⁺.

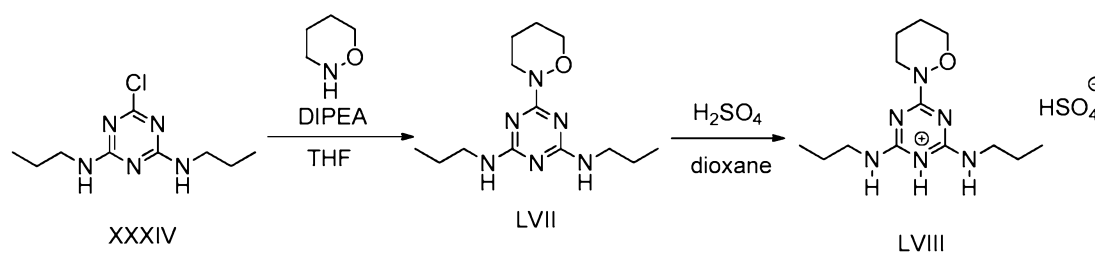
Example 23:N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-isopropyl-hydroxylamine (LV)Example 24:N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-isopropyl-hydroxylamine hydrogen5 sulfate (LVI)Scheme 25*N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-isopropyl-hydroxylamine (LV)*

10 2-Chloro-N-(4, 6-bis(*n*-propylamino)-[1,3,5]triazine (XXXIV) and N-isopropyl-hydroxylamine hydrochloride were reacted as described in Example 13 to yield N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-isopropyl-hydroxylamine (LV) (61% yield). ESI-MS (*m/z*): 269 [M+H]⁺.

*N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-isopropyl-hydroxylamine hydrogen sulfate (LVI)*

15 N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-isopropyl-hydroxylamine hydrogen sulfate (LVI) was prepared from N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-isopropyl-hydroxylamine (LV) and 95% H₂SO₄ as described in Example 20 (95% yield). 200 MHz ¹H NMR (DMSO-*d*₆, ppm) 11.5-11.1 (1H, br s), 10.66-10.40 (1H, m), 8.45 (1H, s), 7.75-7.36 (1H, m), 4.77-4.55 (1H, m), 3.30 -3.16 (4H, m), 1.61-1.44 (4H, m), 1.17 (6H, t, J=7.0 Hz), 0.89 (3H, t, J=7.3 Hz), 0.86 (3H, t, J=7.3 Hz). ESI-MS (*m/z*) 269 [M+H]⁺. M.P.: 154-156°C.

Example 25:6-[1,2]Oxazinan-2-yl-N,N'-dipropyl-[1,3,5]triazine-2,4-diamine (LVII)25 Example 26:6-[1,2]Oxazinan-2-yl-N,N'-di-*n*-propyl-[1,3,5]triazine-2,4-diamine hydrogen sulfate (LVIII)



Scheme 26

6-[1,2]Oxazinan-2-yl-N,N'-di-n-propyl-[1,3,5]triazine-2,4-diamine (LVII)

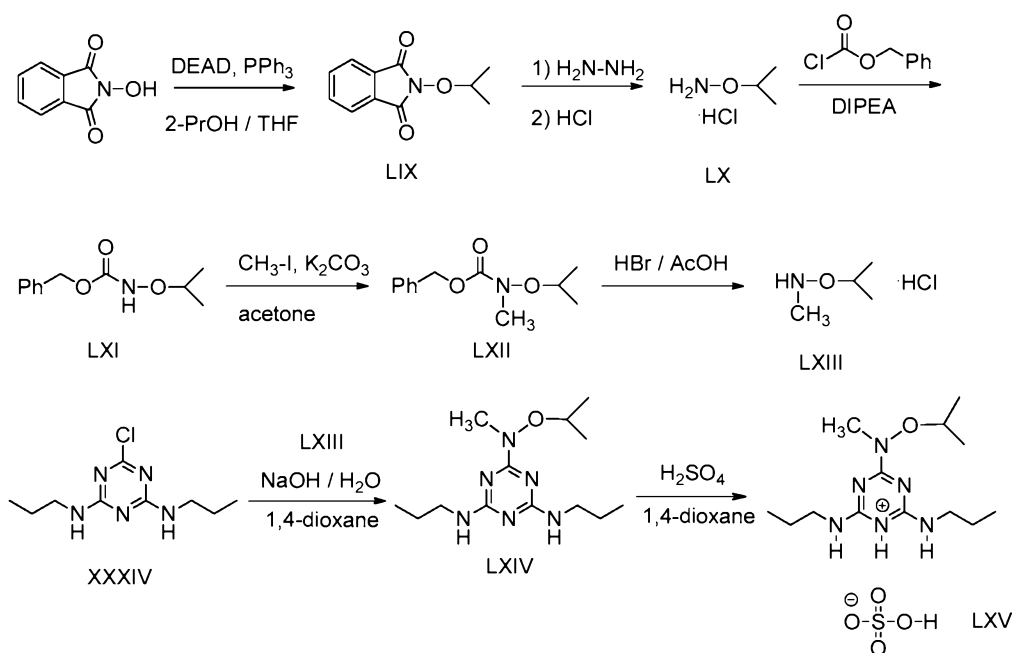
- 5 An ACE[®] pressure tube was charged with 2-chloro-N-(4,6-bis-(n-propylamino)-[1,3,5]triazine (XXXIV) (1.50 g, 6.53 mmol), N-ethyl-diisopropylamine (19.59 mmol), 1,2-oxazinane hydrochloride (1.61 g, 13.06 mmol) and tetrahydrofuran. The reaction mixture was heated at 100 °C for 2 h, then cooled and poured into saturated NaHCO₃ solution (50 mL). The suspension was extracted with
- 10 EtOAc (3 x 25 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using gradient elution from CH₂Cl₂/EtOH (99:1) to CH₂Cl₂/EtOH (95:5) to yield 6-
- 15 [1,2]oxazinan-2-yl-N,N'-di-n-propyl-[1,3,5]triazine-2,4-diamine (LVII) (1.63 g, 89%). ESI-MS (m/z): 281 [M+H]⁺.

6-[1,2]Oxazinan-2-yl-N,N'-di-n-propyl-[1,3,5]triazine-2,4-diamine hydrogen sulfate (LVIII)

- 20 6-[1,2]Oxazinan-2-yl-N,N'-di-n-propyl-[1,3,5]triazine-2,4-diamine hydrogen sulfate (LVIII) was prepared from 6-[1,2]oxazinan-2-yl-N,N'-di-n-propyl-[1,3,5]triazine-2,4-diamine (LVII) and 95% H₂SO₄ as described in Example 20. Quantitative yield was isolated. 400 MHz ¹H-NMR (DMSO-d₆, ppm) 11.6-11.3 (1H, br s), 8.61-8.41 (0.8H, m), 8.18-8.03 (0.2H, m), 7.63-7.28 (1H, m), 4.14-4.08 (2H, m), 3.92-3.81(2H, m, overlapped with water), 3.36-3.19 (4H,m), 1.86-1.78 (2H, m), 1.77-
- 25 1.68 (2H, m), 1.6-1.45 (4H, m), 1.60-1.45 (6H, m). ESI-MS (m/z): 281 [M+H]⁺. M.P.: 134-137°C.

Example 27:N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-N-methyl-hydroxylamine (LXIV)Example 28:5 N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-N-methyl-hydroxylamine hydrogen sulfate (LXV)*2-Isopropoxy-isoindole-1,3-dione (LIX)*

Diethyl azodicarboxylate (14.5 mL, 73.56 mmol) was added dropwise
 10 at 0 °C to a stirred suspension of propan-2-ol (4.7 mL, 61.30 mmol),
 triphenylphosphine (19.30 g, 73.56 mmol), and *N*-hydroxyphthalimide (10.00 g, 61.30
 mmol) in THF (50 mL). The mixture was stirred at room temperature for 20 h and
 evaporated to dryness. The product was purified by flash column chromatography
 using gradient elution from petroleum ether/EtOAc (9:1) to petroleum ether/EtOAc
 15 (5:1) to yield 2-isopropoxy-isoindole-1,3-dione (LIX, 10.92 g, 87%). 400 MHz ¹H
 NMR (DMSO-*d*₆, ppm): 7.86 (4H, s), 4.44 (1H, septet, J=6.2 Hz), 1.28 (6H, d, J=6.2
 Hz).



20

Scheme 27*O-Isopropyl-hydroxylamine hydrochloride (LX)*

A mixture of 2-isopropoxy-isoindole-1,3-dione (LIX, 10.78 g, 52.50 mmol) and hydrazine monohydrate (5.1 mL, 105.00 mmol) in CH₂Cl₂ (60 mL) was stirred at room temperature for 20 h. The reaction mixture was filtered. The filtrate was washed with water (70 mL), brine (70 mL) and dried over Na₂SO₄. After removing the drying agent via filtration, 4M HCl/1,4-dioxane (13.8 mL, 55.00 mmol) was added and the volatiles were removed under reduced pressure to yield O-isopropyl-hydroxylamine hydrochloride (LX, 3.91 g, 67% yield). 400 MHz ¹H NMR (DMSO-d₆, ppm) 11.04 (3H, br s), 4.35 (1H, septet, J=6.2 Hz), 1.21 (6H, d, J=6.2 Hz).

10

O-Benzyl-N-isopropoxy carbamate (LXI)

To a pre-cooled (0 °C) solution of O-isopropyl-hydroxylamine hydrochloride (3.89 g, 34.87 mmol) in CH₂Cl₂ (150 mL) was added N,N-diisopropylethylamine (14.4 mL, 87.18 mmol) and benzyl chloroformate (5.0 mL, 34.87 mmol). The resulting solution was stirred at room temperature for 5 h. At this time the solution was washed twice with saturated aqueous NaHCO₃ (30 mL) and dried over Na₂SO₄. The product was purified by flash column chromatography using gradient elution from petroleum ether/EtOAc (95:5) to petroleum ether/EtOAc (6:1) to yield O-benzyl-N-isopropoxycarbamate (LXI, 4.98 g, 68%). 400 MHz ¹H NMR (DMSO-d₆, ppm) 10.22 (1H, s), 7.42-7.29 (5H, m), 5.07 (2H, s), 3.89 (1H, septet, J=6.2 Hz), 1.11 (6H, d, J=6.2 Hz).

20

O-Benzyl-N-methyl-N-isopropoxy carbamate (LXII)

An ACE[®] pressure tube was charged with benzyl isopropoxycarbamate (4.98 g, 23.80 mmol), anhydrous K₂CO₃ (4.94 g, 35.70 mmol), methyl iodide (6.7 mL, 107.10), and anhydrous acetone (30 mL). The reaction mixture was heated at 70 °C for 24 h. The reaction mixture was filtered, and the acetone was evaporated. The resulting slurry was dissolved in EtOAc, washed with water (3 x 50 mL), dried (Na₂SO₄), and filtered. The solvent was removed to yield benzyl isopropoxy(methyl)carbamate (4.96 g, 93%). 400 MHz ¹H-NMR (DMSO-d₆, ppm) 7.41-7.30 (5H, m), 5.12 (2H, s), 4.08 (1H, septet, J=6.2 Hz), 3.08 (3H, s), 1.12 (6H, d, J=6.2 Hz).

30

O-Isopropyl-N-methyl-hydroxylamine hydrochloride (LXIII)

O-Benzyl-N-methyl-Nisopropoxy carbamate (4.96 g, 22.22 mmol) and 33% HBr/AcOH (45 mL) were stirred at room temperature for 20 min. Saturated solution of NaHCO₃ (400 mL) was added, the suspension was extracted with CH₂Cl₂ (3 x 150 mL). The combined organic extracts were dried over Na₂SO₄. After
5 removal of the drying agent via filtration, 4M HCl/1,4-dioxane (6.7 mL, 26.65 mmol) was added, and the volatiles was removed under reduced pressure to yield O-isopropyl-N-methyl-hydroxylamine hydrochloride (2.09 g, 75%). 400 MHz ¹H NMR (DMSO-d₆, ppm) 12.3-11.7 (2H, br s), 4.49 (1H, septet, J=6.1 Hz), 2.77 (3H, s), 1.12 (6H, d, J=6.1 Hz).

10

*N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-N-methyl-hydroxylamine (LXIV)*

A mixture of 2-chloro-N-(4,6-bis-(*n*-propylamino)-[1,3,5]triazine (XXXIV) (1.65 g, 16.61 mmol), O-isopropyl-N-methyl-hydroxylamine hydrochloride (LXIII, 2.09 g, 16.61 mmol) and NaOH (0.66 g, 16.61 mmol) in 1,4-dioxane (50 mL) and water (5 mL) was heated at 100 °C for 16 h. The volatiles were then removed under reduced pressure. Saturated NaHCO₃ solution (50 mL) was added to the residue and the mixture was extracted with EtOAc (3 x 50 mL). The combined
15 organic extracts were washed with water (50 mL), brine (50 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using gradient elution from CH₂Cl₂/EtOH (99:1) to CH₂Cl₂/EtOH (95:5) to yield N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-N-methyl-hydroxylamine (LXIV, 1.93 g, 95%). ESI-MS (m/z): 283 [M+H]⁺.

20

*N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-N-methyl-hydroxylamine hydrogen sulfate (LXV)*

To a solution N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-N-methyl-hydroxylamine (LXIV, 1.93 g, 6.83 mmol) in 1,4-dioxane (6 mL) at 0°C was added 95% H₂SO₄ (0.36 mL, 6.83 mmol) in a drop-wise manner. The
30 mixture was stirred for 0.5 h at room temperature and then the volatiles were removed under reduced pressure. The residue was co-evaporated with dry toluene (3 x 25 mL) to yield N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-N-methyl-hydroxylamine hydrogen sulfate (~quantitative yield). 400 MHz ¹H-NMR (DMSO-

δ , ppm) 11.3-10.7 (1H, br s), 8.8-8.4 (1H, br s), 8.2-8.0 (0.3H, br s), 8.04-7.65 (0.7H, m), 4.43-4.28 (1H, m), 3.42-3.18 (7H, m), 1.64-1.44 (4H, m), 1.25 (6H, d, $J=6.1$ Hz), 0.94-0.82 (6H, m). ESI-MS (m/z): 283 $[M+H]^+$.

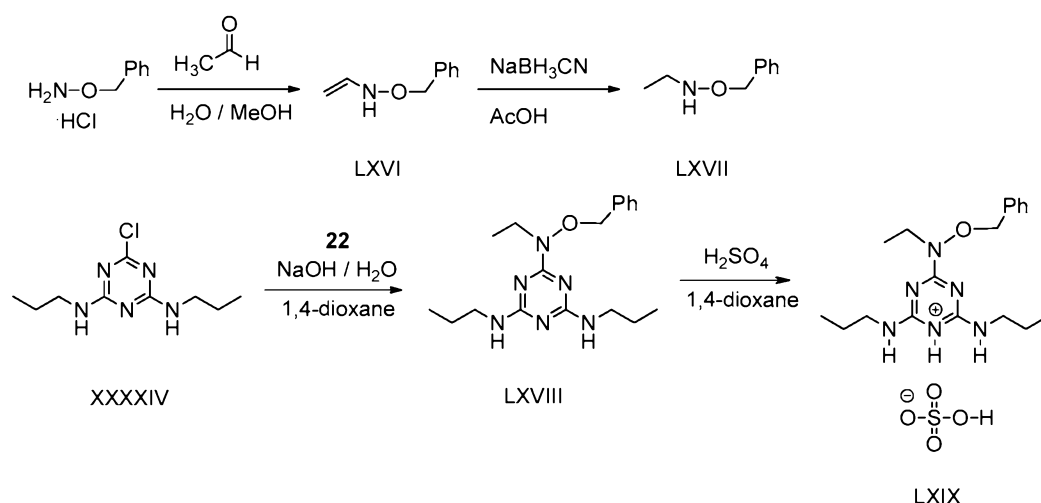
5 Example 29:

O-Benzyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-hydroxylamine (LXVIII)

Example 30:

O-Benzyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-hydroxylamine

10 hydrogen sulfate (LXIX)



Scheme 28

15 O-Benzyl-N-vinyl-hydroxylamine (LXVI)

Acetaldehyde (24.7 mL, 44.2 mmol) was added dropwise to the cooled solution (0 °C) of O-benzyl-hydroxylamine hydrochloride (7.00 g, 43.85 mmol) in water (100 mL) and MeOH (20 mL). The reaction mixture was stirred for 16 h. The volatiles were removed under reduced pressure, and the water suspension was extracted with EtOAc (2 x 75 mL). The combined organic extracts were washed with brine, and then dried over Na_2SO_4 and evaporated to yield O-benzyl-N-vinyl-hydroxylamine (LXVI) in quantitative yield. 400 MHz ^1H NMR ($\text{DMSO}-d_6$, ppm) 7.48 (0.5 H, q, $J=5.8$ Hz), 7.39-7.26 (5H, m), 6.86 (0.5 H, q, $J=5.5$ Hz), 5.06 (1H, s), 4.97 (1H, s), 1.78 (1.5H, d, $J=5.5$ Hz), 1.76 (1.5H, d, $J=5.8$ Hz).

O-Benzyl-N-ethyl-hydroxylamine (LXVII)

To a solution of O-benzyl-N-vinyl-hydroxylamine (LXVI, 6.52 g, 43.70 mmol) in AcOH (10 mL), NaCNBH₃ (11.00 g, 175.05 mmol) was added in portions. The reaction mixture was stirred at room temperature for 1 h. The mixture
 5 was neutralized (pH 7) with 1N NaOH and extracted with EtOAc (3 x 75 mL). The combined organic extracts were washed with saturated NaHCO₃ solution (2 x 100 mL), dried over Na₂SO₄, and purified by flash column chromatography (eluent: petroleum ether/EtOAc (9:1) to petroleum ether/EtOAc (1:4)) to yield O-benzyl-N-ethyl-hydroxylamine (LXVII, 2.10 g, 32%). 400 MHz ¹H NMR (DMSO-d₆, ppm)
 10 7.36-7.24 (5H, m), 6.50 (1H, t, J=6.4 Hz), 4.60 (2H, s), 2.81 (2H, qd, J=7.0, 6.4 Hz), 0.98 (3H, t, J=7.0 Hz).

O-Benzyl-N-(4,6-bis-n-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-hydroxylamine (LXVIII)

15 2-Chloro-N-(4,6-bis-(n-propylamino)-[1,3,5]triazine (XXXIV) and O-benzyl-N-ethyl-hydroxylamine (LXVII) were reacted as described in Example 13 to afford O-benzyl-N-(4,6-bis-n-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-hydroxylamine (LXVIII, 38% yield). 400 MHz ¹H NMR (DMSO-d₆, ppm) 7.51-7.45 (2H, m), 7.40-7.30 (3H, s), 6.97-6.85 (1H, m), 6.79-6.67 (1H, m), 4.97-4.87 (1H, m),
 20 3.72-3.53 (2H, m), 3.23-3.11 (4H, m), 1.56-1.43 (4H, m), 1.13-1.00 (3H, m), 0.89-0.80 (6H, m). ESI-MS (m/z): 345 [M+H]⁺.

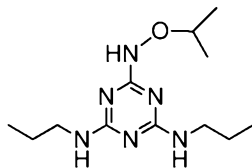
O-Benzyl-N-(4,6-bis-n-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-hydroxylamine hydrogen sulfate (LXIX)

25 O-Benzyl-N-(4,6-bis-n-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-hydroxylamine (LXVIII) was reacted with 95% H₂SO₄ as described in Example 9 to yield O-benzyl-N-(4,6-bis-n-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine hydrogen sulfate (LXIX) in quantitative yield. 400 MHz ¹H NMR (DMSO-d₆, ppm) 12.0-11.0 (1H, br s), 8.7-8.0 (1H, m), 7.57-7.30 (5H, m), 5.07-4.95
 30 (2H, m), 3.89-3.68 (2H, m), 3.39-3.14 (4H, m), 1.63-1.42 (4H, m), 1.23-1.07 (3H, m), 0.94-0.77 (6H, m). ESI-MS (m/z): 345 [M+H]⁺.

Example 31:N-(4,6-Bis-n-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-hydroxylamine (LXX)

Example 32:

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-hydroxylamine hydrogen sulfate (LXXI)



LXX

Scheme 29

5

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-hydroxylamine (LXX)

2-Chloro-N-(4,6-bis-(*n*-propylamino)-[1,3,5]triazine (XXXIV) and O-isopropyl-hydroxylamine hydrochloride were reacted as described in Example 13 (80% yield). ESI-MS (*m/z*): 269 [M+H]⁺.

10

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-hydroxylamine hydrogen sulfate (LXXI)

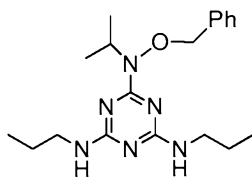
N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-hydroxylamine (LXX) was reacted with 95% H₂SO₄ as described in Example 20 (quantitative yield). 400 MHz ¹H NMR (DMSO-*d*₆, ppm) 11.5-10.7 (1H, m), 8.6-7.5 (3H, m), 4.08 (1H, septet, J=6.2 Hz), 3.38-3.13 (4H, m), 1.61-1.44 (4H, m), 1.21 (6H, d, J=6.2 Hz), 0.94-0.81 (6H, m). ESI-MS (*m/z*): 269 [M+H]⁺.

Example 33:

20 6-((Benzyloxy)(isopropyl)amino)-N²,N⁴-dipropyl-1,3,5-triazine-2,4-diamine (LXXII)

Example 34:

6-((Benzyloxy)(isopropyl)amino)-N²,N⁴-dipropyl-1,3,5-triazine-2,4-diamine hydrogen sulfate (LXXIII)



LXXII

Scheme 30

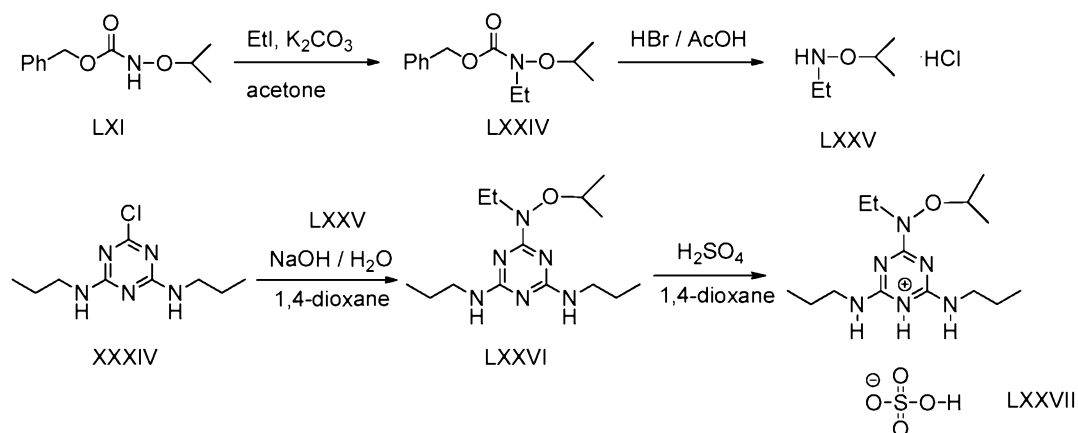
6-((Benzyloxy)(isopropyl)amino)-N²,N⁴-dipropyl-1,3,5-triazine-2,4-diamine (LXXII) was prepared by reacting 2-chloro-N-(4,6-bis-(*n*-propylamino)-[1,3,5]triazine (XXXIV) and O-benzyl-N-isopropyl-hydroxylamine as exemplified in Example 13. The corresponding hydrogen sulfate (LXXIII) was prepared as described in Example 20.

Example 35:

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-O-isopropyl-hydroxylamine (LXXVI)

Example 36:

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-O-isopropyl-hydroxylamine hydrogen sulfate (LXXVII)



Scheme 31

O-Benzyl-N-ethyl-N-isopropoxy-carbamate (LXXIV)

An ACE[®] pressure tube was charged with benzyl isopropoxycarbamate (4.08 g, 19.50 mmol), anhydrous K₂CO₃ (4.04 g, 29.25 mmol), ethyl iodide (7.0 mL, 87.75 mmol), and anhydrous acetone (30 mL). The reaction mixture was heated at 70 °C for 24 h. Ethyl iodide (7.0 mL, 87.75 mmol) and K₂CO₃ (4.04 g, 29.25 mmol) were added and the reaction mixture was heated for 24 h. The reaction mixture was

filtered, and the acetone was evaporated. The resulting slurry was dissolved in EtOAc (150 mL), washed with water (3 x 50 mL), dried (Na₂SO₄), and filtered. The solvent was removed to yield O-benzyl-N-ethyl-N-isopropoxy-carbamate (3.86 g, 83%). 400 MHz ¹H NMR (DMSO-d₆, ppm) 7.41-7.30 (5H, m), 5.12 (2H, s), 4.05 (1H, septet, J=6.2 Hz), 3.46 (2H, q, J=7.0 Hz), 1.12 (6H, d, J=6.2 Hz), 1.06 (3H, t, J=7.0 Hz).

N-Ethyl-O-isopropyl-hydroxylamine hydrochloride (LXXV)

O-Benzyl-N-ethyl-N-isopropoxy-carbamate was reacted with HBr/AcOH as described for the preparation of compound LXIII in Example 27 (yield 71%). 400 MHz ¹H NMR (DMSO-d₆, ppm) 11.7-11.2 (2H, br s), 4.41 (1H, septet, J=6.1 Hz), 3.16 (2H, q, J=7.2 Hz), 1.24 (6H, d, J=6.1 Hz), 1.19 (3H, t, J=7.2 Hz).

N-(4,6-Bis-n-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-O-isopropyl-hydroxylamine (LXXVI)

2-Chloro-N-(4,6-bis-(n-propylamino)-[1,3,5]triazine (XXXIV) was reacted with N-ethyl-O-isopropyl-hydroxylamine hydrochloride (LXXV) as described in Example 13, yielding N-(4,6-bis-n-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-O-isopropyl-hydroxylamine (LXXVI) (88% yield). ESI-MS (m/z): 297 [M+H]⁺.

N-(4,6-Bis-n-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-O-isopropyl-hydroxylamine hydrogen sulfate (LXXVII)

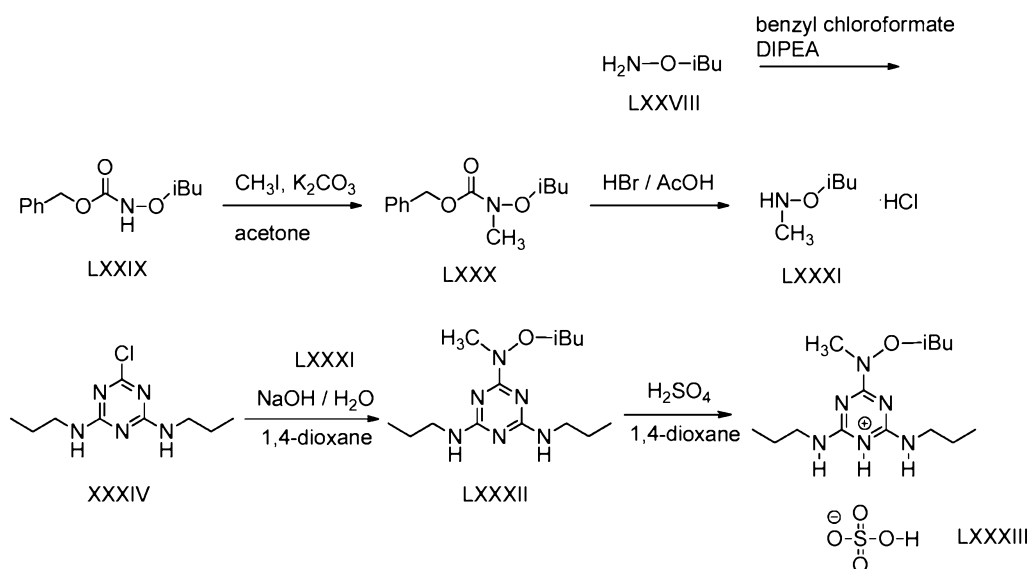
N-(4,6-bis-n-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-O-isopropyl-hydroxylamine (LXXVI) was reacted with 95% H₂SO₄ as described in Example 20 (quantitative yield). 400 MHz ¹H NMR (DMSO-d₆, ppm) 12.0-10.8 (1H, m), 8.7-8.4 (1H, br s), 8.27-7.78 (1H, m), 4.39-4.25 (1H, m), 3.90-3.76 (2H, m), 3.39-3.15 (4H, m), 1.62-1.45 (4H, m), 1.25 (6H, d, J=6.1 Hz), 1.18-1.10 (3H, m), 0.95-0.82 (6H, m). ESI-MS (m/z): 297 [M+H]⁺.

Example 37:

N-(4,6-Bis-n-propylamino-[1,3,5]triazin-2-yl)-O-isobutyl-N-methyl-hydroxylamine (LXXXII)

Example 38:

N-(4,6-Bis-n-propylamino-[1,3,5]triazin-2-yl)-O-isobutyl-N-methyl-hydroxylamine hydrogen sulfate (LXXXIII)



Scheme 32

O-Benzyl-N-isobutoxy carbamate (LXXIX)

5 O-isobutyl-hydroxylamine hydrochloride (LXXVIII) was reacted with benzyl chloroformate as described for the preparation of compound LXI in Example 27, yielding O-benzyl-N-isobutoxy carbamate (LXXIX) (87% yield). 400 MHz ¹H NMR (CDCl₃, ppm) 7.36-7.23 (5H, m), 5.11 (2H, s), 3.58 (2H, d, J=6.6 Hz), 1.89 (1H, septet, J=6.7 Hz), 0.86 (6H, d, J=6.7 Hz).

10

O-Benzyl-N-methyl-N-isobutoxy carbamate (LXXX)

 O-Benzyl-N-isobutoxycarbamate was reacted with methyl iodide, as described for the preparation of compound LXII in Example 27, affording O-benzyl-N-methyl-N-isobutoxycarbamate in 78% yield. 400 MHz ¹H-NMR (DMSO-d₆, ppm) 7.41-7.30 (5H, m), 5.12 (2H, s), 3.59 (2H, d, J=6.6 Hz), 3.09 (3H, s), 1.80 (1H, septet, J=6.7 Hz), 0.87 (6H, d, J=6.7 Hz).

15

O-Isobutyl-N-methyl-hydroxylamine hydrochloride (LXXXI)

 O-Benzyl-N-methyl-N-isobutoxycarbamate was reacted with HBr/AcOH as described for the preparation of compound LXIII in Example 27 (38% yield). 200 MHz ¹H NMR (DMSO-d₆, ppm) 12.5-11.4 (2H, br s), 3.84 (2H, d, J=6.6 Hz), 2.81 (3H, s), 1.90 (1H, septet, J=6.7 Hz), 0.89 (6H, d, J=6.7 Hz).

20

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-*O*-isobutyl-*N*-methyl-hydroxylamine (LXXXII)

2-Chloro-*N*-(4,6-bis-(*n*-propylamino)-[1,3,5]triazine (XXXIV) was reacted with *O*-isobutyl-*N*-methyl-hydroxylamine hydrochloride as described in Example 13, affording LXXXII in 82% yield. ESI-MS (*m/z*) 297 [M+H]⁺.

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-*O*-isobutyl-*N*-methyl-hydroxylamine hydrogen sulfate (LXXXIII)

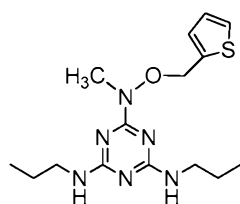
N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-*O*-isobutyl-*N*-methyl-hydroxylamine (LXXXII) was reacted with 95% H₂SO₄ as described in Example 20 (quantitative yield). 400 MHz ¹H-NMR (DMSO-*d*₆, ppm) 12.0-10.7 (1H, br s), 8.7-7.6 (2H, m), 3.82-3.72 (2H, m), 3.41-3.20 (7H, m), 2.11-1.82 (1H, m), 1.62-1.44 (4H, m), 1.00-0.82 (12H, m). ESI-MS (*m/z*): 297 [M+H]⁺.

15 Example 39:

6-(Methyl(thiophen-2-ylmethoxy)amino)-*N*²,*N*⁴-di-*n*-propyl-1,3,5-triazine-2,4-diamine (LXXXIV)

Example 40:

20 6-(Methyl(thiophen-2-ylmethoxy)amino)-*N*²,*N*⁴-di-*n*-propyl-1,3,5-triazine-2,4-diamine hydrogen sulfate (LXXXV)



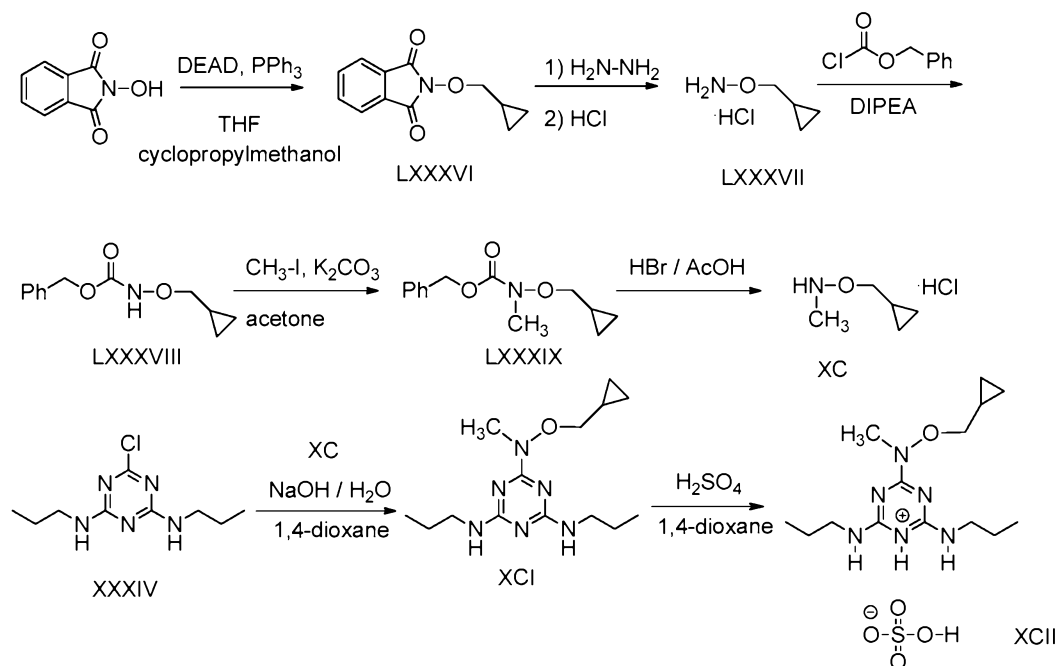
LXXXIV

Scheme 33

6-(Methyl(thiophen-2-ylmethoxy)amino)-*N*²,*N*⁴-di-*n*-propyl-1,3,5-triazine-2,4-diamine (LXXXIV) may be prepared by reacting 2-chloro-*N*-(4,6-bis-(*n*-propylamino)-[1,3,5]triazine (XXXIV) and *O*-(thiophen-2-yl-methyl)-*N*-methyl-hydroxylamine as exemplified in Example 13.

Example 41:

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-*O*-cyclopropylmethyl-*N*-methyl-hydroxylamine (XCI)

Example 42:N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-cyclopropylmethyl-N-methyl-hydroxylamine hydrogen sulfate (XCII)

5

Scheme 34*2-Cyclopropylmethoxy-isoindole-1,3-dione (LXXXVI)*

N-Hydroxyphthalimide and cyclopropyl-methanol were reacted as described for compound LIX in Example 27, to afford LXXXVI in 87% yield. 400 MHz ¹H NMR (DMSO-*d*₆, ppm) 7.86 (4H, s), 3.97 (2H, d, *J*=7.4 Hz), 1.22-1.11 (1H, m), 0.61-0.48 (2H, m), 0.34-0.22 (2H, m).

O-Cyclopropylmethyl-hydroxylamine hydrochloride (LXXXVII)

2-Cyclopropylmethoxy-isoindole-1,3-dione was reacted with hydrazine as described for compound LX in Example 27 (LXXXVII, in 67% yield). 400 MHz ¹H NMR (DMSO-*d*₆, ppm) 10.95 (3H, br s), 3.83 (2H, d, *J*=7.4 Hz), 1.12-1.01 (1H, m), 0.62-0.50 (2H, m), 0.35-0.24 (2H, m).

O-Benzyl-N-cyclopropylmethoxy carbamate (LXXXVIII)

O-Cyclopropylmethyl-hydroxylamine hydrochloride was reacted with benzyl chloroformate as described for compound LXI in Example 27 (LXXXVIII, in

88% yield). 400 MHz ¹H-NMR (DMSO-d₆, ppm) 10.37 (1H, br s), 7.41-7.30 (5H, m), 5.08 (2H, s), 3.54 (2H, d, J=7.2 Hz), 1.06-0.92 (1H, m), 0.54-0.41 (2H, m), 0.25-0.13 (2H, m).

5 *O-Benzyl-N-methyl-N-cyclopropylmethoxy-carbamate (LXXXIX)*

O-Benzyl N-cyclopropylmethoxy carbamate and methyl iodide were reacted as described for compound LXII in Example 27 (LXXXIX, in 95% yield). 400 MHz ¹H NMR (DMSO-d₆, ppm) 7.42-7.30 (5H, m), 5.11 (2H, s), 3.62 (2H, d, J=7.2 Hz), 3.11 (3H, s), 1.06-0.93 (1H, m), 0.54-0.41 (2H, m), 0.26-0.13 (2H, m).

10

O-Cyclopropylmethyl-N-methyl-hydroxylamine hydrochloride (XC)

O-Benzyl-N-methyl-N- cyclopropylmethoxy carbamate was reacted with HBr/AcOH as described for compound LXIII in Example 27, yielding XC in 77% yield. 400 MHz ¹H NMR (DMSO-d₆, ppm) 11.96 (2H, br s), 3.91 (2H, d, J=7.4 Hz), 2.80 (3H, s), 1.13-1.01 (1H, m), 0.63-0.50 (2H, m), 0.37-0.25 (2H, m).

15

N-(4,6-Bis-n-propylamino-[1,3,5]triazin-2-yl)-O-cyclopropylmethyl-N-methyl-hydroxylamine (XCI)

2-Chloro-N-(4, 6-bis-(n-propylamino)-[1,3,5]triazine (XXXIV) was reacted with O-cyclopropylmethyl-N-methyl-hydroxylamine hydrochloride (XC) as described in Example 13, yielding (XCI) in 99% yield. 400 MHz ¹H NMR (DMSO-d₆, ppm) 6.91-6.77 (1H, m), 6.75-6.58 (1H, m), 3.77-3.64 (2H, m), 3.21-3.09 (7H, m), 1.54-1.41 (4H, m), 1.11-1.00 (1H, m), 0.88-0.80 (6H, m), 0.56-0.44 (2H, m), 0.32-0.20 (2H, m). ESI-MS (m/z) 295 [M+H]⁺.

25

N-(4,6-Bis-n-propylamino-[1,3,5]triazin-2-yl)-O-cyclopropylmethyl-N-methyl-hydroxylamine hydrogen sulfate (XCII)

N-(4,6-bis-n-propylamino-[1,3,5]triazin-2-yl)-O-cyclopropylmethyl-N-methyl-hydroxylamine (XCI) was reacted with 95% H₂SO₄ as described in Example 20, yielding (XCII) in quantitative yield. 400 MHz ¹H-NMR (DMSO-d₆, ppm) 11.6-11.0 (1H, br s), 8.7-8.4 (0.7H, br s), 8.2-8.0 (0.3H, br s), 7.89-7.42 (1H, m), 3.88-3.77 (2H, m), 3.42-3.18 (7H, m), 1.62-1.45 (4H, m), 1.24-1.13 (1H, m), 0.95-0.82 (6H, m), 0.61-0.52 (2H, m), 0.38-0.28 (2H, m). ESI-MS (m/z) 295 [M+H]⁺.

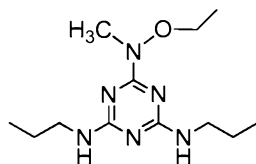
30

Example 43:

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-ethyl-N-methyl-hydroxylamine
(XCVI)

Example 44:

- 5 N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-ethyl-N-methyl-hydroxylamine
hydrogen sulfate (XCVII)



XCVI

Scheme 35*tert*-Butyl ethoxycarbamate (XCIII)

- 10 A solution of saturated Na₂CO₃ solution (45.0 mL) was added dropwise at room temperature to a solution of O-ethyl-hydroxylamine (1.76 g, 18.0 mmol) and di-*tert*-butyl dicarbonate (5.13 g, 23.67 mmol) in dichloromethane (45.0 mL) and stirred for 24 h. Water was added, the mixture pH was adjusted to 2 by adding 6N HCl, and the resulting system was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over Na₂SO₄ and evaporated. The crude product was purified by flash column chromatography using gradient elution from petroleum ether/EtOAc (98:2) to petroleum ether/EtOAc (95:5) to yield *tert*-butyl ethoxycarbamate (XCIII) (2.62 g, 90%). 400 MHz ¹H NMR (DMSO-*d*₆, ppm) 9.89 (1H, s) 3.72 (2H, q, J=7.0 Hz) 1.40 (9H, s) 1.10 (3H, t, J=7.0 Hz).

20

tert-Butyl ethoxy(methyl)carbamate (XCIV)

- A solution of *tert*-butyl ethoxycarbamate (XCIII, 2.48 g, 15.38 mmol) in DMF (10 mL) was added dropwise to the suspension of 60% sodium hydride (0.66 g, 16.92 mmol) in DMF (5 mL) at 0 °C. After 30 min. methyl iodide (1.95 mL, 31.32 mmol) in DMF (10 mL) was added, and the reaction mixture was stirred at room temperature for 24 h. Water (100 mL) was added and the product was extracted with ethyl acetate (3 x 50 mL), dried over Na₂SO₄, and concentrated *in vacuo* to yield *tert*-butyl ethoxy(methyl)carbamate (XCIV, 2.34 g, 87%). 400 MHz ¹H NMR (DMSO-*d*₆, ppm) 3.81 (2H, q, J=7.0 Hz), 3.00 (3H, s), 1.41 (9H, s), 1.12 (3H, t, J=7.0 Hz).

30

O-Ethyl-N-methyl-hydroxylamine hydrochloride (XCV)

A solution of 4M HCl/1,4-dioxane (25 mL) was added in portions to *tert*-butyl ethoxy(methyl)carbamate (XCIV, 2.34 g, 13.35 mmol) at 0°C. The mixture was stirred at room temperature for 4 h. The volatiles removed *in vacuo* and the
5 residue was triturated with ethyl ether and filtered to yield a solid (O-ethyl-N-methyl-hydroxylamine hydrochloride, XCV, 1.35 g, 91%).

*N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-ethyl-N-methyl-hydroxylamine (XCVI)*

10 2-Chloro-N-(4, 6-bis-(*n*-propylamino)-[1,3,5]triazine (XXXIV) was reacted with O-ethyl-N-methyl-hydroxylamine hydrochloride as described in Example 13, to yield XCVI in 93% yield. ESI-MS (m/z) 269 [M+H]⁺.

*N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-ethyl-N-methyl-hydroxylamine hydrogen sulfate (XCVII)*

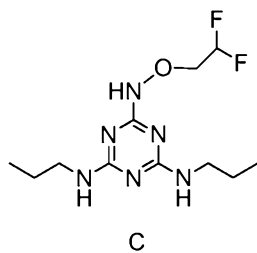
15 N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-ethyl-N-methyl-hydroxylamine (XCVI) was reacted with 95% H₂SO₄ as described in Example 20, to afford (XCVII) in 91% yield. 400 MHz ¹H NMR (DMSO-d₆, ppm) 11.7-10.8 (1H, br s), 8.79-7.34 (2H, m), 4.09-3.98 (2H, m), 3.40-3.20 (7H, m), 1.61-1.46 (4H, m),
20 1.27 (3H, t, J=7.1 Hz), 0.94-0.84 (6H, m). 400 MHz ¹H NMR (D₂O, ppm) 3.99-3.88 (2H, m), 3.34-3.13 (7H, m), 1.52-1.39 (4H, m), 1.14 (3H, t, J=7.1 Hz), 0.76 (6H, t, J=7.5 Hz). ESI-MS (m/z): 269 [M+H]⁺. M.P.: 84-86°C.

Example 45:

25 N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-(2,2-difluoro-ethyl)-hydroxylamine (C)

Example 46:

N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-(2,2-difluoro-ethyl)-hydroxylamine hydrogen sulfate (CI)



Scheme 36

2-(2,2-Difluoro-ethoxy)-isoindole-1,3-dione (XCVIII)

N-Hydroxyphthalimide and 2,2-difluoro-ethanol were reacted as described for compound LXI in Example 27, affording XCVIII in 52% yield. 400 MHz ¹H NMR (DMSO-d₆, ppm) 7.92-7.85 (4H, m), 6.34 (1H, tt, J=54.4, 3.9 Hz), 4.46 (2H, td, J=14.1, 3.9 Hz).

O-(2,2-Difluoro-ethyl)-hydroxylamine hydrochloride (XCIX)

2-(2,2-Difluoro-ethoxy)-isoindole-1,3-dione was reacted with hydrazine as described for compound LX in Example 27, affording XCIX in 73% yield. 400 MHz ¹H NMR (DMSO-d₆, ppm) 12.3-10.3 (3H, br s), 6.38 (1H, tt, J=54.0, 3.3 Hz), 4.34 (2H, td, J=14.7, 3.3 Hz).

N-(4,6-Bis-n-propylamino-[1,3,5]triazin-2-yl)-O-(2,2-difluoro-ethyl)-hydroxylamine (C)

2-Chloro-N-(4, 6-bis-(*n*-propylamino)-[1,3,5]triazine (XXXIV) was reacted with O-(2,2-difluoro-ethyl)-hydroxylamine hydrochloride as described in Example 13, affording C in 59% yield. 400 MHz ¹H NMR (DMSO-d₆, ppm) 9.91-9.56 (1H, m), 7.00-6.90 (1H, m), 6.89-6.67 (1H, m), 6.48-6.13 (1H, m), 4.12-3.98 (2H, m), 3.20-3.09 (4H, m), 1.53-1.41 (4H, m), 0.88-0.80 (6H, m). ESI-MS (m/z) 291 [M+H]⁺.

N-(4,6-Bis-n-propylamino-[1,3,5]triazin-2-yl)-O-(2,2-difluoro-ethyl)-hydroxylamine hydrogen sulfate (CI)

N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-(2,2-difluoro-ethyl)-hydroxylamine (C, 1.02 g, 3.51 mmol) was reacted with 95% H₂SO₄ (0.19 mL, 3.51 mmol) in diethyl ether (3 mL) at 0°C. Two drops of EtOH were added, and the resultant crystals were filtered, washed with diethyl ether, and dried to yield N-(4,6-

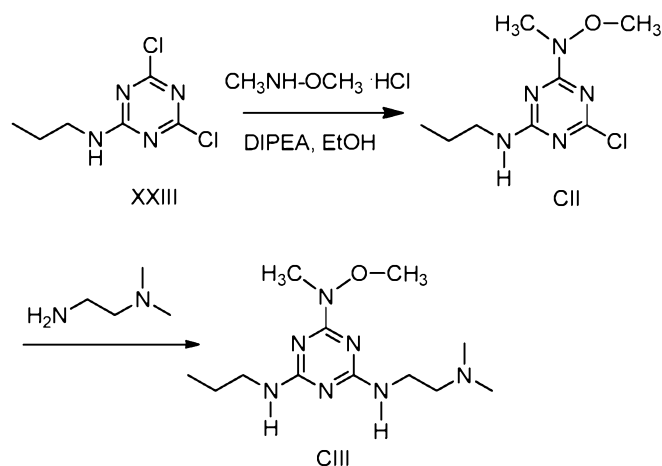
bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-(2,2-difluoro-ethyl)-hydroxylamine hydrogen sulfate (CI) (1.26 g, 93%). 400 MHz ^1H NMR (DMSO- d_6 , ppm) 11.8-10.5 (1H, m) 8.8-8.4 (0.3H, br s) 8.36-7.53 (1.7H, m) 6.50-6.08 (1H, m) 4.28-4.07 (2H, m) 3.39-3.13 (4H, m) 1.64-1.42 (4H, m) 0.97-0.78 (6H, m). ESI-MS (m/z) 291 $[\text{M}+\text{H}]^+$.
 5 M.P.: 91-93°C.

Example 47:

4-N-(2-Dimethylaminoethyl)amino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CIII)

10 Example 48:

4-N-(2-Dimethylaminoethyl)amino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CIV)



Scheme 37

15 2-Chloro-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CII)

2,4-Dichloro-N-(6-*n*-propylamino)-[1,3,5]triazine (XXIII) (18 g, 87 mmol) was dissolved in acetone (100 mL) and poured into ice-water (50 mL) to form a very fine suspension. A solution of N,O-dimethylhydroxylamine hydrochloride (9.3 g, 95 mmol) in water (30 mL) was added, while keeping the temperature at 0 °C (ice bath). To this mixture, 2N NaOH (44 mL, 88 mmol) was added dropwise at a rate adjusted to keep the temperature between 0 °C and 5 °C. The reaction was stirred for 30 min at ambient temperature and for additional 60 min at 50 °C. The resultant precipitate was filtered off, and washed with water (3 x 25 mL). After drying over
 25 calcium chloride under high vacuum, 2-chloro-N-(6-*n*-propylamino)-[1,3,5]triazin-2-

yl)-N,O-dimethyl-hydroxylamine (CII, 12 g, 60%) was isolated as a white powder.
LCMS (ESI) $m/z = 232$ (M+H)⁺.

5 *4-N-(2-Dimethylaminoethyl)amino-6-N-(n-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CIII)*

A mixture of 2-chloro-6-N-(n-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CII, 1.5 g, 6.5 mmol), N,N-dimethylethane-1,2-diamine (3.5 g, 39 mmol) and DIPEA (2.5 g, 20 mmol) in EtOH (30 mL) was heated at 100 °C for 16 h. The solvent was then removed under reduced pressure. The residue was
10 dissolved in EtOAc (80 mL), washed with water (2 x 50 mL) and then with a brine solution (50 mL) and lastly, dried over Na₂SO₄. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (DCM/MeOH=20/1 to 5/1) to yield 4-N-(2-dimethylaminoethyl)amino-6-N-(n-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (620 mg, 33%).

15

4-N-(2-Dimethylaminoethyl)amino-6-N-(n-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CIV)

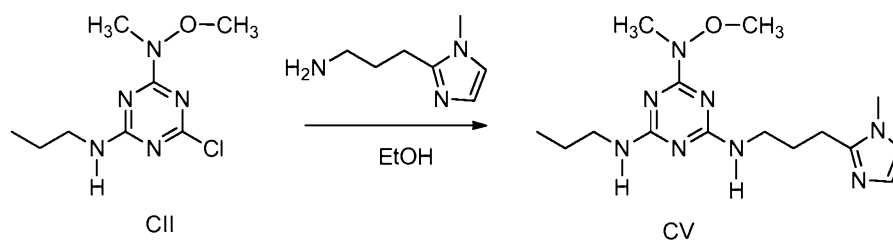
4-N-(2-dimethylaminoethyl)amino-6-N-(n-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (610 mg, 2.1 mmol) was dissolved
20 in H₂O (10 mL) and 0.5 M aqueous HCl solution (6.6 mL) and the solution was lyophilized to yield 4-N-(2-dimethylaminoethyl)amino-6-N-(n-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CIV, 630 mg) as a colorless oil. LCMS (ESI) $m/z = 284$ (M+H)⁺. ¹H NMR (500 MHz, DMSO) δ (ppm) 10.55-10.88 (br, 1H), 8.70-9.10 (m, 2H), 4.37-4.43 (m, 5H), 3.76-3.87 (m, 7H), 2.84-
25 2.88 (m, 6H), 1.60-1.64 (m, 2H), 0.94-1.02 (m, 3H).

Example 49:

4-N-(3-(1-N-Methylimidazol-2-yl)-propyl)-amino-6-N-(n-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CV)

30 Example 50:

4-N-(3-(1-N-Methylimidazol-2-yl)-propyl)-amino-6-N-(n-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CVI)



Scheme 38

4-N-(3-(1-N-Methylimidazol-2-yl)-propyl)-amino-6-N-(n-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CV)

2-Chloro-6-N-(n-propylamino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CII) (400 mg, 2.9 mmol), DIPEA (5.16 g, 40 mmol) and 3-(1-methyl-1H-imidazol-2-yl)propan-1-amine (J. Heterocyclic Chem., 2005, 42:1011-15) (732 mg, 3.2 mmol) in EtOH (50 mL) were heated at 100 °C for 16 h. After this time, the solvent was removed under reduced pressure. The residue was dissolved in DCM/MeOH (400 mL/200 mL), washed with water (50 mL) then dried over Na₂SO₄. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (DCM/MeOH=50/1 to 10/1) to yield 4-N-(3-(1-N-methylimidazol-2-yl)-propyl)-amino-6-N-(n-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CV, 210 mg, 22%).

4-N-(3-(1-N-Methylimidazol-2-yl)-propyl)-amino-6-N-(n-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CVI)

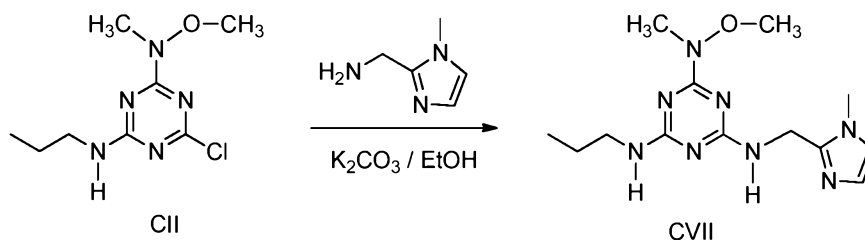
4-N-(3-(1-N-methylimidazol-2-yl)-propyl)-amino-6-N-(n-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CV) (210 mg, 0.63 mmol) was dissolved in H₂O (10 mL) and 0.5 M aqueous HCl solution (1.3 mL), and the solution was lyophilized to yield 4-N-(3-(1-N-methylimidazol-2-yl)-propyl)-amino-6-N-(n-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CVI, 210 mg) as a yellow oil. LCMS (ESI) m/z = 335 (M+H)⁺. ¹H NMR (500 MHz, DMSO) δ (ppm) 14.40-14.55 (br, 1H), 8.60-8.80 (m, 2H), 7.57-7.62 (m, 2H), 3.77-3.83 (m, 6H), 3.28-3.42 (m, 7H), 2.80-2.84 (m, 2H), 1.95-2.10 (m, 2H), 1.53-1.56 (m, 2H), 0.89-0.93 (m, 3H).

Example 51:

4-N-(1-N-Methylimidazol-2-yl)-methylamino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CVII)

Example 52:

4-N-(1-N-Methylimidazol-2-yl)-methylamino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CVIII)



Scheme 39

10 4-N-(1-N-Methylimidazol-2-yl)-methylamino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CVII)

2-Chloro-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CII) (1 g, 4.5 mmol), (1-methyl-1H-imidazol-2-yl)methanamine (600 mg, 5.4 mmol) and K₂CO₃ (1.24 g, 9 mmol) in EtOH (50 mL) were heated at 100 °C
 15 for 16 h. The reaction mixture was filtered, and the volatiles were removed under reduced pressure. The residue was dissolved in EtOAc (100 mL), washed with water (30 mL) and then with a brine solution (30 mL), and lastly dried over Na₂SO₄. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (DCM/MeOH=20/1 to 8/1) to yield 4-N-(1-N-
 20 methylimidazol-2-yl)-methylamino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CVII, 650 mg, 47%).

4-N-(1-N-Methylimidazol-2-yl)-methylamino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CVIII)

25 4-N-(1-N-methylimidazol-2-yl)-methylamino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CVII, 650 mg, 2.1 mmol) was dissolved in H₂O (10 mL) and 0.5 M aqueous HCl solution (6.3 mL). The resultant solution was subjected to lyophilization to yield 4-N-(1-N-methylimidazol-2-yl)-methylamino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine
 30 hydrochloride (CVIII, 389 mg) as a colorless oil. LCMS (ESI) m/z = 307 (M+H)⁺.

¹H NMR (500 MHz, DMSO) δ (ppm) 14.65-14.85 (br, 1H), 8.70-9.20 (m, 2H), 7.62-7.70 (m, 2H), 4.87-4.91 (m, 2H), 3.75-3.89 (m, 9H), 3.31-3.40 (m, 3H), 1.55-1.56 (m, 2H), 0.85-0.96 (m, 3H).

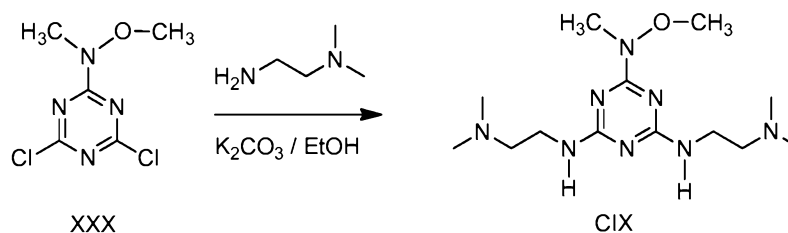
5 Example 53:

4,6-Bis-(N-(2-dimethylaminoethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CIX)

Example 54:

4,6-Bis-(N-(2-dimethylaminoethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-

10 hydroxylamine hydrochloride (CX)



Scheme 40

4,6-Bis-(N-(2-dimethylaminoethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-

15 *hydroxylamine (CIX)*

N-(4,6-Dichloro[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXX) (7 g, 33.5 mmol), N,N-dimethyl-ethane-1,2-diamine (6.05 g, 68.7 mmol) and K₂CO₃ (10.2 g, 73.7 mmol) in THF (250 mL) were heated at 70 °C for 5 h, after which time the solvent was removed under reduced pressure. The residue was

20 purified by reverse flash column chromatography to yield 4,6-bis-(N-(2-dimethylaminoethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (270 mg, 3%).

4,6-Bis-(N-(2-dimethylaminoethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-

25 *hydroxylamine hydrochloride (CX)*

4,6-Bis-(N-(2-dimethylaminoethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (270 mg, 0.86 mmol) was dissolved in H₂O (10 mL) and 0.5 M aqueous HCl solution (2 mL), and the resultant solution was lyophilized to yield

30 4,6-bis-(N-(2-dimethylaminoethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (290 mg) as a colorless oil. LCMS (ESI) m/z = 313

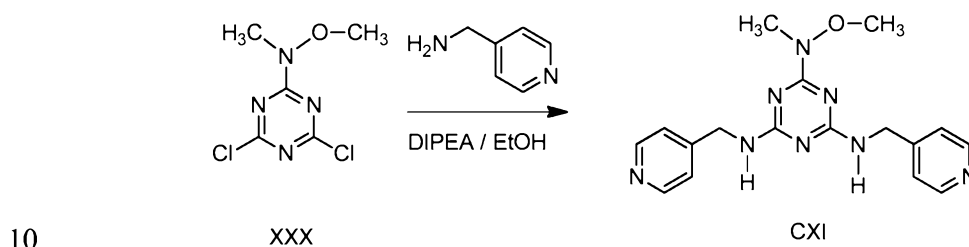
(M+H)⁺. ¹H NMR (500 MHz, DMSO) δ (ppm) 10.20-10.60 (br, 1H), 7.17-7.25 (m, 2H), 3.54-3.76 (m, 7H), 3.01-3.25 (m, 7H), 2.72 (s, 12H).

Example 55:

5 4,6-Bis-(N-(pyridin-4-ylmethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CXI)

Example 56:

4,6-Bis-(N-(pyridin-4-ylmethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CXII)



Scheme 41

4,6-Bis-(N-(pyridin-4-ylmethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CXI)

15 N-(4,6-Dichloro[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXX) (1 g, 4.78 mmol), pyridin-4-ylmethanamine (1.14, 10.52 mmol) and DIPEA (1.85 g, 14.34 mmol) in EtOH (80 mL) were heated at 100 °C for 16 h, after which the solvent was removed under reduced pressure. The crude product was purified by flash chromatography to yield 4,6-bis-(N-(pyridin-4-ylmethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CXI) (450 mg, 27%).

20

4,6-Bis-(N-(pyridin-4-ylmethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CXII)

25 4,6-Bis-(N-(pyridin-4-ylmethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CXI) (450 mg, 1.28 mmol) was dissolved in H₂O (10 mL) and 0.5 M aqueous HCl solution (3.84 mL), and the resultant solution was lyophilized to yield 4,6-bis-(N-(pyridin-4-ylmethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine_hydrochloride (497 mg) as a yellow solid. LCMS (ESI) m/z = 353 (M+H)⁺. ¹H NMR (500 MHz, MeOD) δ (ppm) 8.79-8.89 (m, 4H), 7.98-8.20 (m, 4H), 5.04 (s, 2H), 4.85 (s, 2H), 3.90-3.95 (m, 3H), 3.50 (s, 1H), 3.33 (s, 2H).

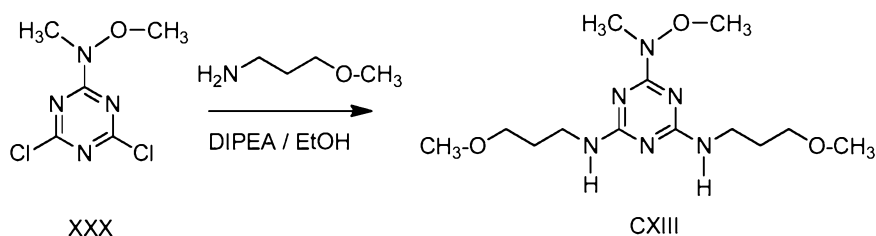
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Example 57:

4,6-Bis-[N-(3-methoxy-*n*-propyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CXIII)

5 Example 58:

4,6-Bis-[N-(3-methoxy-*n*-propyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride salt (CXIV)

Scheme 42

10

*4,6-Bis-[N-(3-methoxy-*n*-propyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CXIII)*

N-(4,6-Dichloro[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXX) (1 g, 4.78 mmol), 3-methoxypropan-1-amine (936 mg, 10.52 mmol) and
 15 DIPEA (1.85 g, 14.34 mmol) in EtOH (50 mL) were heated at 100 °C for 16 h, after which time the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (200 mL), washed with water (50 mL) and then with a brine solution (50 mL) and lastly dried over Na₂SO₄. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography
 20 (pet ether/ethyl acetate = 5/1 to 1/2) to yield 4,6-bis-[N-(3-methoxy-*n*-propyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CXIII) (1.4 g, 93%).

*4,6-Bis-[N-(3-methoxy-*n*-propyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CXIV)*

25 4,6-Bis-[N-(3-methoxy-*n*-propyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CXIII, 1.4 g, 4.46 mmol) was dissolved in H₂O (10 mL) and 0.5 M aqueous HCl solution (13.4 mL), and the resultant solution was lyophilized to yield 4,6-bis-[N-(3-methoxy-*n*-propyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrochloride (1.56 g) as a colorless oil. LCMS (ESI) *m/z* = 315

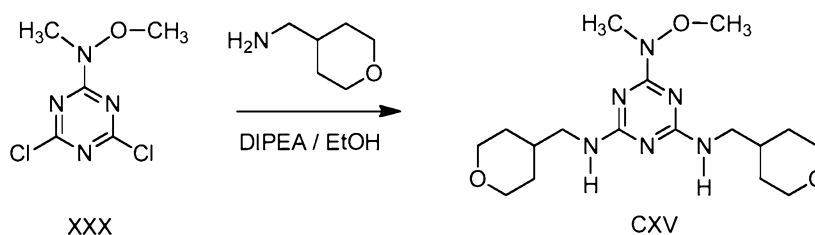
(M+H)⁺. ¹H NMR (500 MHz, DMSO) δ (ppm) 12.10-12.60 (br, 1H), 8.55-8.74 (m, 2H), 3.75-3.86 (m, 3H), 3.35-3.45 (m, 11H), 3.22-3.25 (m, 5H), 2.77 (s, 1H), 1.72-1.76 (m, 4H).

5 Example 59:

4,6-Bis-[N-(tetrahydropyran-4-ylmethyl)amino]-[1,3,5]triazin-2-yl]-N,O-dimethyl-hydroxylamine (CXV)

Example 60:

10 4,6-Bis-[N-(tetrahydropyran-4-ylmethyl)amino]-[1,3,5]triazin-2-yl]-N,O-dimethyl-hydroxylamine hydrochloride (CXVI)



Scheme 43

15 4,6-Bis-[N-(tetrahydropyran-4-ylmethyl)amino]-[1,3,5]triazin-2-yl]-N,O-dimethyl-hydroxylamine (CXV)

N-(4,6-Dichloro[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXX) (1 g, 4.78 mmol), (tetrahydro-2H-pyran-4-yl)methanamine (1.21 g, 10.52 mmol) and DIPEA (1.85 g, 14.34 mmol) in EtOH (50 mL) were heated at 100 °C for 16 h, after which time the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (200 mL), washed with water (50 mL) and then with a brine solution (50 mL) and lastly dried over Na₂SO₄. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PE/EA=5/1 to 1/1) to afford 4,6-bis-[N-(tetrahydropyran-4-ylmethyl)amino]-[1,3,5]triazin-2-yl]-N,O-dimethyl-hydroxylamine (CXV) (1.5 g, 85%).

25

4,6-Bis-[N-(tetrahydropyran-4-ylmethyl)amino]-[1,3,5]triazin-2-yl]-N,O-dimethyl-hydroxylamine hydrochloride (CXVI)

4,6-Bis-[N-(tetrahydropyran-4-ylmethyl)amino]-[1,3,5]triazin-2-yl]-N,O-dimethyl-hydroxylamine (CXV) (1.5 g, 4.1 mmol) was dissolved in H₂O (10

mL) and 0.5 M aqueous HCl solution (12.3 mL), and the resultant solution was lyophilized to yield 4,6-bis-[N-(tetrahydropyran-4-ylmethyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (CXVI) hydrochloride (1.65 g) as a white solid.

LCM: (ESI) $m/z = 367 (M+H)^+$. ^1H NMR (500 MHz, DMSO) δ (ppm) 12.30-12.70

(br, 1H), 8.65-8.80 (m, 2H), 3.77-3.86 (m, 7H), 3.20-3.35 (m, 11H), 1.75-1.78 (m, 2H), 1.56-1.58 (m, 4H), 1.20-1.23 (m, 4H).

Example 61:

N-(5,8,11-Trioxa-2,14,16,18,19-pentaazabicyclo[13.3.1]nonadeca-

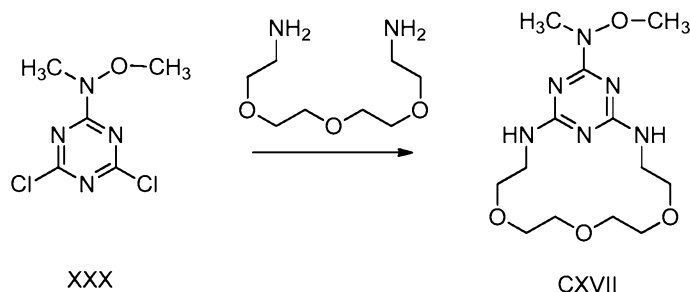
1(18),15(19),16(17)-trien-17-yl)-N,O-dimethylhydroxylamine (CXVII)

Example 62:

N-(5,8,11-Trioxa-2,14,16,18,19-pentaazabicyclo[13.3.1]nonadeca-

1(18),15(19),16(17)-trien-17-yl)-N,O-dimethylhydroxylamine hydrochloride

(CXVIII)



15

Scheme 44

N-(5,8,11-Trioxa-2,14,16,18,19-pentaazabicyclo[13.3.1]nonadeca-

1(18),15(19),16(17)-trien-17-yl)-N,O-dimethylhydroxylamine (CXVII)

20 N-(4,6-Dichloro[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXX) (1.63 g, 7.8 mmol) in EtOH (100 mL) was added to 2,2'-(2,2'-oxybis(ethane-2,1-diyl))bis(oxy))diethanamine (*Org. Biomol. Chem.* 2005, 3:2255-61) (1.5 g, 7.8 mmol) and DIPEA (2.01 g, 15.6 mmol). The reaction was heated at 100 °C for 3 h, after which time the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (200 mL), washed with water (2 × 100 mL) and then with a brine solution (100 mL) and lastly dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (DCM/MeOH=50/1 to 20/1) to yield N-(5,8,11-trioxa-2,14,16,18,19-

25

pentaazabicyclo[13.3.1]nonadeca-1(18),15(19),16(17)-trien-17-yl)-N,O-dimethylhydroxylamine (CXVII) (700 mg) as a colourless oil (yield 27%).

N-(5,8,11-Trioxa-2,14,16,18,19-pentaazabicyclo[13.3.1]nonadeca-

5 1(18),15(19),16(17)-trien-17-yl)-N,O-dimethylhydroxylamine hydrochloride (CXVIII)

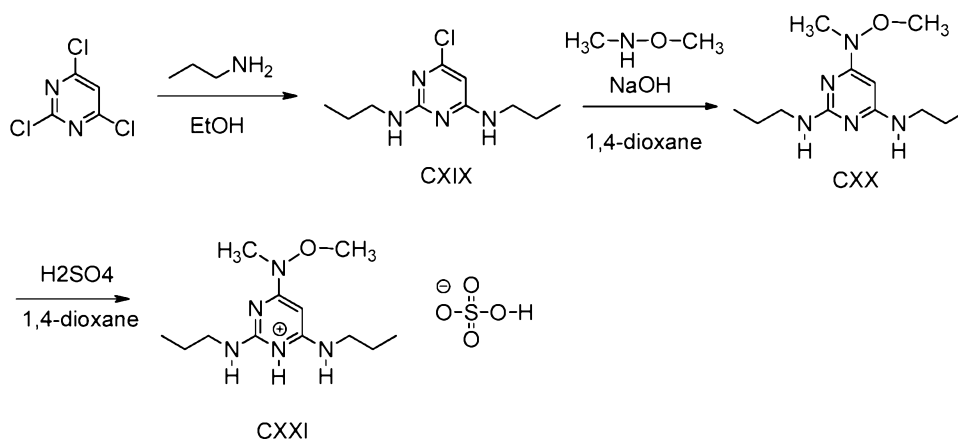
N-(5,8,11-Trioxa-2,14,16,18,19-pentaazabicyclo[13.3.1]nonadeca-1(18),15(19),16(17)-trien-17-yl)-N,O-dimethylhydroxylamine (CXVII) (700 mg, 2.1 mmol) was dissolved in H₂O (10 mL) and 0.5 M aqueous HCl solution (4.3 mL), and the resultant solution was lyophilized to yield N-(5,8,11-trioxa-2,14,16,18,19-
10 pentaazabicyclo[13.3.1]nonadeca-1(18),15(19),16(17)-trien-17-yl)-N,O-dimethylhydroxylamine hydrochloride (CXVIII) (750) mg as a colorless oil. LCMS: (ESI) $m/z = 329 (M+H)^+$. ¹H NMR (500 MHz, DMSO) δ (ppm) 11.50-12.60 (br, 1H), 8.61 (s, 2H), 3.77 (s, 3H), 3.30-3.62 (m, 16H), 3.30 (s, 3H).

15 Example 63:

2,6-Bis-(N-*n*-propylamino)-[1,3]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine (CXX)

Example 64:

20 2,6-Bis-(N-*n*-propylamino)-[1,3]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (CXXI)



Scheme 45

4-Chloro-2,6-bis-[N-n-propylamino]-1,3-pyrimidine (CXIX)

25 2,4,6-Trichloro-pyrimidine (5.00 g, 27.26 mmol) and *n*-propylamine (13.5 mL, 163.56 mmol) in EtOH were heated at 60 °C for 24 h and then cooled. The

volatiles were removed under reduced pressure. Water (100 mL) was added and the resulting suspension was extracted with CH₂Cl₂ (3 x 75 mL). The combined organic extracts were washed with water (150 mL), then with a brine solution (100 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure to yield 4-chloro-2,6-bis-[N-*n*-propylamino]-1,3-pyrimidine (CXIX) (5.78 g, 93%). 200 MHz ¹H-NMR (DMSO-d₆, ppm) 7.26-7.04 (1H, m) 7.04-6.81 (1H, m) 5.69 (1H, s) 3.26-3.01 (4H, m) 1.60-1.36 (4H, m) 0.87 (3H, t, J=7.4 Hz) 0.85 (3H, t, J=7.4 Hz); ESI-MS (m/z) 229, 231 [M+H]⁺.

10 (2,6-Bis-N-[*n*-propylamino]-pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine (CXX)
4-Chloro-2,6-bis-[N-*n*-propylamino]-1,3-pyrimidine (CXIX) (5.78 g, 25.27 mmol), N,O-dimethylhydroxylamine hydrochloride (4.93 g, 50.54 mmol) and NaOH (2.02 g, 50.54 mmol) in 1,4-dioxane (400 mL) and water (20 mL) were heated at 60 °C for 24 h. N,O-Dimethylhydroxylamine hydrochloride (4.93 g, 50.54 mmol)
15 and NaOH (3.03 g, 75.81 mmol) were added to the reaction mixture and heating was continued for 3 days at 110°C. The volatiles were removed under reduced pressure. Saturated NaHCO₃ solution (50 mL) was added to the residue and the mixture was extracted with CH₂Cl₂ (3 x 75 mL). The combined organic extracts were washed with water (150 mL) and dried over Na₂SO₄. The solvent was removed under reduced
20 pressure, and the residue was purified by flash column chromatography (CH₂Cl₂/EtOH (25/1)) to yield (2,6-bis-N-[*n*-propylamino]-pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine (CXX) (1.2 g, 19%). 200 MHz ¹H-NMR (DMSO-d₆, ppm) 6.57-6.45 (1H, m) 6.13 (1H, t, J= 5.5 Hz) 5.34 (1H, s) 3.59 (3H, s) 3.20-3.04 (4H, m) 3.03 (3H, s) 1.58-1.37 (4H, m) 0.87 (3H, t, J=7.1 Hz) 0.84 (3H, t, J=7.1 Hz).

25 (2,6-Bis-N-[*n*-propylamino]-pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (CXXI)

(2,6-Bis-N-[*n*-propylamino]-pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine (1.20 g, 4.74 mmol) in 1,4-dioxane (15 mL) was treated with 95%
30 H₂SO₄ (0.27 mL, 4.74 mmol) in a dropwise manner at 0°C. The mixture was stirred at room temperature for 0.5 h and then the volatiles were removed under reduced pressure. The resulting residue was co-evaporated with dry toluene (3 x 5 mL) to yield (2,6-bis-N-[*n*-propylamino]-pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (CXXI) in quantitative yield. 400 MHz H-NMR (DMSO-d₆, ppm)

11.3-10.5 (1H, m), 8.29 (0.4H, br s), 7.38 (0.6H, br s), 5.48-5.20 (1H, m), 3.70 (3H, s), 3.36-3.21 (5H, m), 3.20-3.08 (2H, m), 1.61-1.48 (4H, m), 0.9 (6H, t, J=7.4 Hz).
ESI-MS (m/z) 254 [M+H]⁺; melting point: 123-126 °C.

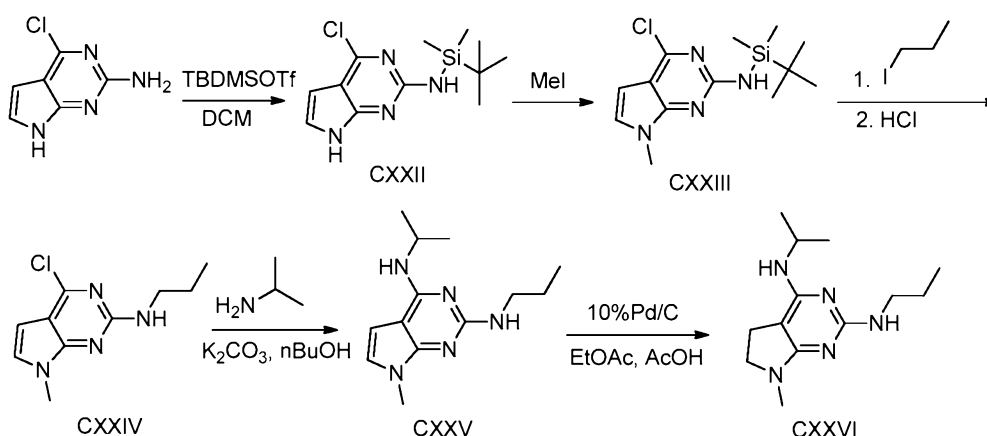
5 Example 65:

2-(*n*-Propyl)amino-4-(*i*-propylamino-7-methyl-pyrrolidino[2,3-*d*]pyrimidine (CXXVI)

Example 66:

2-(*n*-Propyl)amino-4-(*i*-propylamino-7-methyl-pyrrolidino[2,3-*d*]pyrimidine

10 hydrochloride (CXXVII)



Scheme 46

2-(*t*-Butyl-dimethylsilyl)amino-4-chloro-7H-pyrrolo[2,3-*d*]pyrimidine (CXXII)

- 15 To a dichloromethane solution (100 mL) of 2-amino-4-chloro-7H-pyrrolo[2,3-*d*]pyrimidine (8.7 g, 52 mmol) was added Et₃N (26 g, 260 mmol) and the mixture was stirred at -30 °C. After this time, TBDMSOTf (15.1 g, 57.2 mmol) was added in a slow dropwise manner and the resultant reaction was stirred at ambient temperature for 1.5 h. The observed solid material completely dissolved to form a
- 20 light brown solution. The mixture was then quenched with 1 N NaOH (100 mL) and extracted with DCM (250 mL). The organic layer was washed with H₂O (150 mL) and then with a brine solution (150 mL) and dried over Na₂SO₄. The solvents were removed in vacuo and the residue was purified by flash column chromatography (PE/EtOAc=10/1 to 5/1) to afford 2-(*t*-butyl-dimethylsilyl)amino-4-chloro-7H-
- 25 pyrrolo[2,3-*d*]pyrimidine (CXXII, 11.4 g, 79%) as a light yellow solid. LCMS: (ESI) m/z = 283 (M+H)⁺.

2-(t-Butyl-dimethylsilyl)amino-4-chloro-7-methyl-pyrrolo[2,3-d]pyrimidine (CXXIII)

2-(t-Butyl-dimethylsilyl)amino-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (CXXII) (700 mg, 2.5 mmol), 0.18 mL (3.5 mmol) of methyl iodide in DMF (10 mL),
5 and K₂CO₃ (552 mg, 4 mmol) were reacted at ambient temperature for 15 h. After addition of H₂O (10 mL), the reaction was extracted with EtOAc (100 mL), and the organic layer was washed with a brine solution (10 mL), and dried over Na₂SO₄. The solvents were removed in vacuo, and the residue was purified by flash column chromatography (PE/EtOAc=10/1 to 5/1) to afford 2-(t-butyl-dimethylsilyl)amino-4-chloro-7-methyl-pyrrolo[2,3-d]pyrimidine (CXXIII) (750 mg, 100%) as a light yellow
10 oil. LCMS (ESI) m/z = 297 (M+H)⁺.

2-(n-Propyl)amino-4-chloro-7-methyl-pyrrolo[2,3-d]pyrimidine (CXXIV)

Under a nitrogen atmosphere 2-(t-butyl-dimethylsilyl)amino-4-chloro-7-methyl-pyrrolo[2,3-d]pyrimidine (CXXIII, 5.0 g, 17 mmol) and 1-iodopropane (4.3 g, 25 mmol) were dissolved in DMF (20 mL). The reaction mixture was cooled to 0 °C with vigorous stirring, then NaH (1 g of a 60% dispersion in mineral oil, 21 mmol) was added. The mixture was stirred for 10 min. and water (50 mL) was slowly added to quench the reaction. The aqueous solution was extracted with EtOAc (200 mL),
20 and the organic layer was washed with water (50 mL) and with a brine solution (50 mL), and lastly, dried over anhydrous Na₂SO₄. After evaporation of volatiles, a yellow oily residue (5.7 g) was isolated. The residue was dissolved in Et₂O (50 mL) and concentrated hydrochloric acid (10 mL) was added at 0 °C with stirring. The mixture was reacted for an additional 10 min. After this time, the solution was
25 extracted with EtOAc (200 mL) and 1N NaOH (200 mL). The organic layer was washed with H₂O (150 mL) and then with a brine solution (150 mL) and lastly, dried over Na₂SO₄. The solvents were removed in vacuo and the resultant residue was purified by flash column chromatography (PE/EtOAc=10/1 to 5/1) to afford 2-(n-propyl)amino-4-chloro-7-methyl-pyrrolo[2,3-d]pyrimidine (3.78 g, 100%) of the
30 desired product as a yellow solid. LCMS: (ESI) m/z = 225 (M+H)⁺.

2-(n-Propyl)amino-4-(i-propyl)amino-7-methyl-pyrrolo[2,3-d]pyrimidine (CXXV)

To a solution of 2-(n-propyl)amino-4-chloro-7-methyl-pyrrolo[2,3-d]pyrimidine (1.6 g, 7.1 mmol) in n-butanol (10 mL) was added potassium carbonate

(4.9 g, 35.5 mmol), followed by propan-2-amine (632 mg, 10.7 mmol). The mixture was stirred in an autoclave equipped with a stirrer at 140 °C for 16 h. After cooling to room temperature, water was added (20 mL), and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water and then
 5 with a brine solution, and lastly dried over anhydrous Na₂SO₄. The volatiles were removed in vacuo and the residue was purified by flash column chromatography (PE/EtOAc=3/1) to yield 2-(*n*-propyl)amino-4-(*i*-propyl)amino-7-methyl-pyrrolo[2,3-*d*]pyrimidine (1.2 g, 75%) as a yellow solid. LCMS: (ESI) *m/z* = 248 (M+H)⁺.

10 *2-(n-Propyl)amino-4-(i-propylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine (CXXVI)*

To the solution of 2-(*n*-propyl)amino-4-(*i*-propyl)amino-7-methyl-pyrrolo[2,3-*d*]pyrimidine (CXXV, 1.0 g, 4 mmol) in EtOAc (50 mL) were added 10% Pd/C (1.0 g) and AcOH (2.43 g, 40 mmol). The mixture was attached to a hydrogenation apparatus and the system was evacuated and then refilled with
 15 hydrogen. The reaction was stirred at ambient temperature for 48 h. After this time, the mixture was filtered over 10 g of silica-gel on a glass-filter. The filtrate was concentrated and the residue was purified by flash column chromatography (DCM/MeOH=50/1 to 10/1) to yield 2-(*n*-propyl)amino-4-(*i*-propylamino-7-methyl-pyrrolidino[2,3-*d*]pyrimidine (CXXVI, 500 mg, 50%) as a yellow solid.

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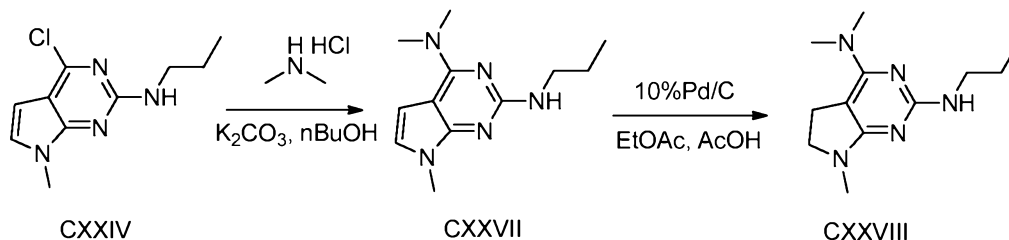
2-(n-Propyl)amino-4-(i-propylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine hydrochloride (CXXVII)

The isolated free amine (CXXVI, 500 mg, 2 mmol) was dissolved in H₂O (10 mL) and 0.5 M aqueous HCl solution (4 mL), and the solution was
 25 lyophilized to yield 2-(*n*-propyl)amino-4-(*i*-propylamino-7-methyl-pyrrolidino[2,3-*d*]pyrimidine hydrochloride (CXXVII, 525 mg) as a brown solid. LCMS (ESI) *m/z* = 250 (M+H)⁺. ¹H NMR (500 MHz, MeOD) δ (ppm) 3.80 (s, 1H), 3.58 (t, *J* = 8.5 Hz, 2H), 3.23-3.29 (m, 2H), 2.88 (s, 3H), 2.77 (t, *J* = 8.5 Hz, 2H), 1.52-1.56 (m, 2H), 1.15 (d, *J* = 6.5 Hz, 6H), 0.89 (d, *J* = 7.5 Hz, 3H).

30

Example 67:

2-(n-Propyl)amino-4-dimethylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine (CXXVIII)

Example 68:2-(*n*-Propyl)amino-4-dimethylamino-7-methyl-pyrrolidino[2,3-*d*]pyrimidine hydrochloride (CXXIX)

5

Scheme 472-(*n*-Propyl)amino-4-dimethylamino-7-methyl-pyrrolo[2,3-*d*]pyrimidine (CXXVII)

To 2-(*n*-propyl)amino-4-chloro-7-methyl-pyrrolo[2,3-*d*]pyrimidine (1.0 g, 4.5 mmol) (CXXIV) in *n*-butanol (20 mL) was added potassium carbonate (3.7 g, 27 mmol) and dimethylamine hydrochloride (1.0 g (22 mmol)). The mixture was stirred in an autoclave equipped with a stirrer at 120 °C for 16 h. After cooling to room temperature, water was added (20 mL), and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water and then with a brine solution, and dried over anhydrous Na₂SO₄. The solvents were removed in vacuo and the residue was purified by flash column chromatography (PE/EtOAc=6/1) to yield 2-(*n*-propyl)amino-4-dimethylamino-7-methyl-pyrrolo[2,3-*d*]pyrimidine (CXXVII, 800 mg, 76%) as a yellow solid. LCMS (ESI) *m/z* = 234 (M+H)⁺.

20 2-(*n*-Propyl)amino-4-dimethylamino-7-methyl-pyrrolidino[2,3-*d*]pyrimidine (CXXVIII)

To the solution of 2-(*n*-propyl)amino-4-dimethylamino-7-methyl-pyrrolo[2,3-*d*]pyrimidine (CXXVII, 800 mg, 3.4 mmol) in EtOAc (30 mL) was added 10% Pd/C (1.0 g) and AcOH (3 mL), and the mixture was attached to a hydrogenation apparatus. The system was evacuated and then refilled with hydrogen. The mixture was stirred at ambient temperature for 48 h. The mixture was filtered through 10 g of silica-gel on a glass-filter. The filtrate was concentrated and the residue was purified by flash column chromatography (EtOAc/MeOH=25/1) to yield 2-(*n*-propyl)amino-4-dimethylamino-7-methyl-pyrrolidino[2,3-*d*]pyrimidine (CXXVIII, 600 mg, 75%).

30

2-(n-Propyl)amino-4-dimethylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine hydrochloride (CXXIX)

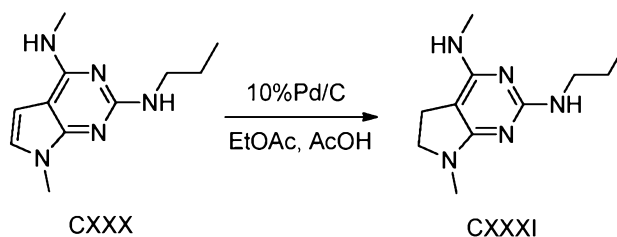
2-(*n*-Propyl)amino-4-dimethylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine (CXXVIII, 600 mg, 2.6 mmol) was dissolved in H₂O (10 mL) and 0.5 M aqueous HCl solution (5.2 mL), and the solution was lyophilized to yield 2-(*n*-propyl)amino-4-dimethylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine hydrochloride (CXXIX, 600 mg) as a yellow solid. LCMS (ESI) *m/z* = 236 (M+H)⁺. ¹H NMR (500 MHz, MeOD) δ (ppm) 3.66 (t, *J* = 9.0 Hz, 2H), 3.40 (t, *J* = 7.0 Hz, 2H), 3.33 (s, 1H), 3.23 (t, *J* = 9.5 Hz, 2H), 3.17 (s, 5H), 3.00 (s, 3H), 1.63-1.67 (m, 2H), 1.00 (t, *J* = 7 Hz, 3H).

Example 69:

2-(*n*-Propyl)amino-4-methylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine (CXXXI)

Example 70:

15 2-(*n*-Propyl)amino-4-methylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine hydrochloride (CXXXII)



Scheme 48

2-(n-Propyl)amino-4-methylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine (CXXXI)

20 To a solution of 2-(*n*-propyl)amino-4-methylamino-7-methyl-pyrrolo[2,3-d]pyrimidine (CXXX) (2.0 g, 9.13 mmol) in EtOAc (50 mL) was added 10% Pd/C (2.1 g) and AcOH (8 mL), and the mixture was attached to a hydrogenation apparatus. The system was evacuated and refilled with hydrogen. The mixture was stirred at ambient temperature for 48 h. The mixture was filtered through 10 g of silica-gel on a glass-filter. The filtrate was concentrated and the residue was purified by flash column chromatography (DCM/MeOH=60/1 to 10/1) to yield 2-(*n*-propyl)amino-4-methylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine (CXXXI, 700 mg, 43%) as a yellow solid.

2-(*n*-Propyl)amino-4-methylamino-7-methyl-pyrrolidino[2,3-*d*]pyrimidine hydrochloride (CXXXII)

2-(*n*-Propyl)amino-4-methylamino-7-methyl-pyrrolidino[2,3-*d*]pyrimidine (CXXX, 700 mg, 3.2 mmol) was dissolved in H₂O (10 mL) and 0.5 M aqueous HCl solution (7 mL), and the solution was lyophilized to yield 2-(*n*-propyl)amino-4-methylamino-7-methyl-pyrrolidino[2,3-*d*]pyrimidine (717 mg) as a brown solid. LCMS: (ESI) $m/z = 222$ (M+H)⁺. ¹H NMR (500 MHz, MeOD) δ (ppm) 3.50 (t, $J=8.5$, 2H), 3.22 (t, $J=7.0$ Hz, 2H), 2.79 (s, 6H), 2.68 (t, $J=9.0$ Hz, 2H), 1.43-1.51 (m, 2H), 0.81 (t, $J=8.0$ Hz, 3H).

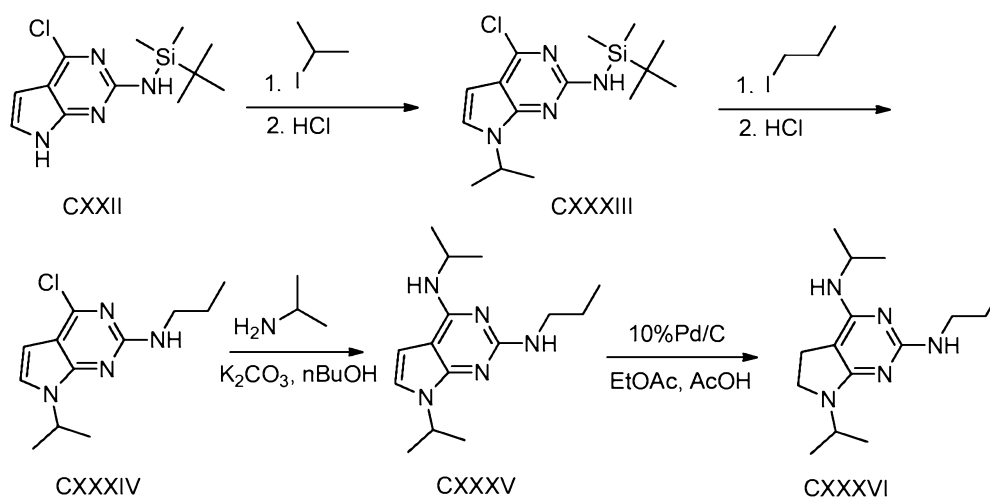
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Example 71:

2-(*n*-Propyl)amino-4-(*i*-propyl)amino-7-*i*-propyl-pyrrolidino[2,3-*d*]pyrimidine (CXXXVI)

Example 72:

15 2-(*n*-Propyl)amino-4-(*i*-propyl)amino-7-*i*-propyl-pyrrolidino[2,3-*d*]pyrimidine hydrochloride salt (CXXXVII)



Scheme 49

20 2-(*t*-Butyl-dimethylsilyl)amino-4-chloro-7-*i*-propyl-pyrrolo[2,3-*d*]pyrimidine (CXXXIII)

2-(*t*-Butyl-dimethylsilyl)amino-4-chloro-7H-pyrrolo[2,3-*d*]pyrimidine (CXXXII) (5 g, 17.7 mmol), 2-iodopropane (4.5 g, 26.6 mmol) and K₂CO₃ (4.3 g, 26.6 mmol) in DMF (20 mL) were reacted at ambient temperature for 25 15 h. After addition of H₂O (50 mL) to the reaction mixture, the aqueous solution

was extracted with EtOAc (300 mL) and the organic layer was washed with a brine solution (50 mL) and dried with Na₂SO₄. The solvents were removed in vacuo and the residue was purified by flash column chromatography (pet ether/EtOAc=10/1 to 5/1) to afford 2-(*t*-butyl-dimethylsilyl)amino-4-chloro-7-*i*-propyl-pyrrolo[2,3-
5 d]pyrimidine (CXXXIII, 5.7 g, 100%) as a light yellow oil. LCMS: (ESI) m/z = 325 (M+H)⁺.

2-(n-Propyl)amino-4-chloro-7-i-propyl-pyrrolo[2,3-d]pyrimidine (CXXXIV)

Under nitrogen atmosphere, 2-(*t*-butyl-dimethylsilyl)amino-4-
10 chloro-7-*i*-propyl-pyrrolo[2,3-d]pyrimidine (5.7 g, 17.6 mmol) and 1-iodopropane (4.5 g (26.4 mmol) were dissolved in DMF (20 mL). The reaction mixture was cooled to 0 °C with vigorous stirring, and NaH (1.06 g of a 60% dispersion in mineral oil, 26.4 mmol) of (60%) was added. The mixture was stirred for 10 min, and then water (50 mL) was slowly added to quench the reaction. The mixture was extracted
15 with EtOAc (300 mL) and the organic layer was washed with water (50 mL) and then with a brine solution (50 mL), and lastly, dried over anhydrous Na₂SO₄. After evaporation of the solvents, a yellow oily residue was isolated (6.5 g). The residue was dissolved in Et₂O (50 mL), concentrated hydrochloric acid (10 mL) was added at 0 °C with stirring, and the mixture was stirred for an additional 10 min. After the
20 reaction was completed, the solution was extracted with EtOAc (200 mL) and 1N NaOH (200 mL). The organic layer was washed with H₂O (150 mL) and then with a brine solution (150 mL) and dried over Na₂SO₄. The solvents in vacuo and the residue was purified by flash column chromatography (PE/EtOAc=10/1 to 5/1) to yield 2-(*n*-propyl)amino-4-chloro-7-*i*-propyl-pyrrolo[2,3-d]pyrimidine (CXXXIV, 4.5
25 g, 100%) as a yellow solid. LCMS (ESI) m/z = 253 (M+H)⁺.

2-(n-Propyl)amino-4-(i-propyl)amino-7-i-propyl-pyrrolo[2,3-d]pyrimidine (CXXXV)

To 2-(*n*-propyl)amino-4-chloro-7-*i*-propyl-pyrrolo[2,3-d]pyrimidine (CXXXIV, 3.0 g, 12 mmol) in *n*-butanol (10 mL) was added propan-2-amine (1.05 g,
30 18 mmol) and potassium carbonate (2.5 g, 18 mmol). The resulting mixture was stirred in an autoclave equipped with a stirrer at 140 °C for 16 h. After cooling to room temperature, water was added (20 mL), and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water and then with a brine solution and dried over anhydrous Na₂SO₄. After the solvents were

removed in vacuo, the residue was purified by flash column chromatography (PE/EtOAc=5/1 to 3/1) to yield 2-(*n*-propyl)amino-4-(*i*-propyl)amino-7-*i*-propyl-pyrrolo[2,3-*d*]pyrimidine (CXXXV, 1.2 g, 36%) as a yellow solid. LCMS: (ESI) m/z = 276 (M+H)⁺.

5

2-(n-Propyl)amino-4-(i-propyl)amino-7-i-propyl-pyrrolidino[2,3-d]pyrimidine
(CXXXVI)

To a solution of 2-(*n*-propyl)amino-4-(*i*-propyl)amino-7-*i*-propyl-pyrrolo[2,3-*d*]pyrimidine (1.0 g, 3.6 mmol) in EtOAc (10 mL) were added 10% Pd/C (1.0 g) and AcOH (2.43 g, 40 mmol). The mixture was attached to a hydrogenation apparatus. The system was evacuated and refilled with hydrogen gas. The mixture was stirred at ambient temperature for 48 h, and filtered through 10 g of silica-gel on a glass-filter. The filtrate was concentrated and the residue was purified by flash column chromatography (DCM/MeOH=100/1 to 20/1) to yield 2-(*n*-propyl)amino-4-(*i*-propyl)amino-7-*i*-propyl-pyrrolidino[2,3-*d*]pyrimidine (CXXXVI) (800 mg, 79%) as a yellow solid.

15

2-(n-Propyl)amino-4-(i-propyl)amino-7-i-propyl-pyrrolidino[2,3-d]pyrimidine hydrochloride (CXXXVII)

20

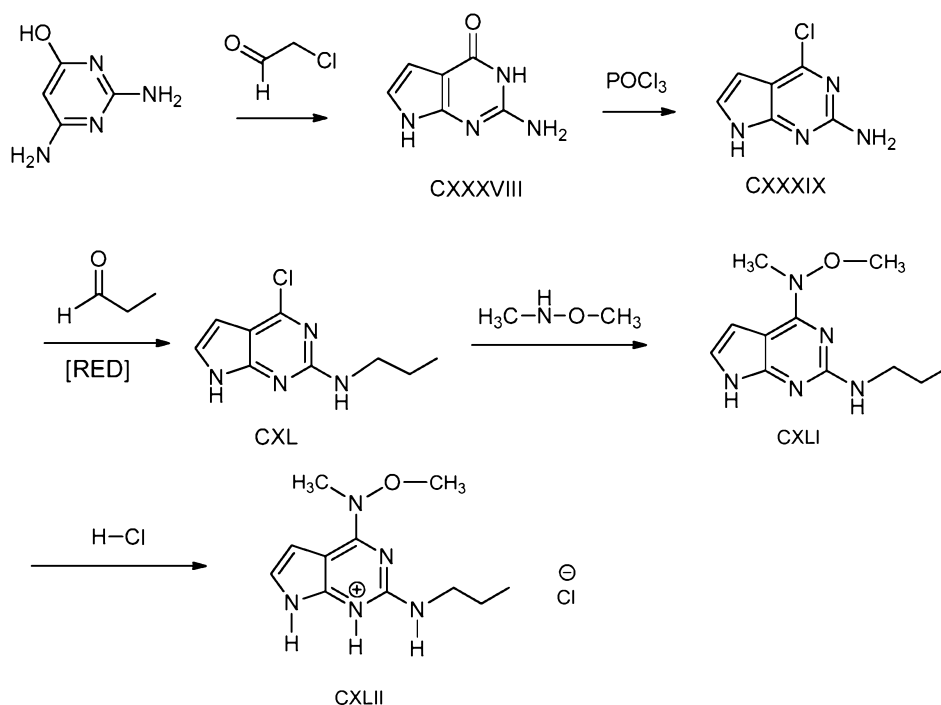
2-(*n*-Propyl)amino-4-(*i*-propyl)amino-7-*i*-propyl-pyrrolo[2,3-*d*]pyrimidine (200 mg, 0.72 mmol) was dissolved in H₂O (10 mL) and 0.5 M aqueous HCl solution (1.5 mL) and then the solution was lyophilized to yield 2-(*n*-propyl)amino-4-(*i*-propyl)amino-7-*i*-propyl-pyrrolidino[2,3-*d*]pyrimidine hydrochloride (225 mg, 95%) as a yellow solid. LCMS (ESI) m/z = 278 (M+H)⁺. ¹H NMR (500 MHz, MeOD) δ (ppm) 4.36 (s, 1H), 3.90 (s, 1H), 3.67 (t, J = 8.5 Hz, 2H), 3.30 (t, J = 7.5 Hz, 2H), 2.84 (t, J = 8.5 Hz, 2H), 1.60-1.66 (m, 2H), 1.24 (d, J = 6.0 Hz, 6H), 1.21 (d, J = 6.0 Hz, 6H), 0.98 (t, J = 7.5 Hz, 3H).

25

Example 73: N-(2-Propylamino-7H-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine (CXLI)

30

Example 74: N-(2-Propylamino-7H-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CXLII)



Scheme 50

2-Amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3d]pyrimidine (CXXXVIII)

- 5 To the solution of 2,4-diamino-6-hydroxypyrimidine (50 g, 397 mmol) in H₂O (750 mL) was added 2-chloroacetaldehyde (40% in H₂O, 85 g, 437 mmol) in a dropwise manner at 0 °C. The mixture was stirred at 65°C for 2 h and then heated at 100°C until the reaction was complete. The resultant solids were filtered and the remaining residue was heated at reflux in EtOH (750 mL). The additional
- 10 solids were filtered and the mother liquor was concentrated to afford 2-amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3d]pyrimidine(CXXXVIII) as a yellow solid 40 g (~67%, ~70% purity). LCMS (ESI) m/z = 151 (M+H)⁺.

2-Amino-4-chloro-7H-pyrrolo[2,3d]pyrimidine (CXXXIX)

- 15 2-Amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3d]pyrimidine (CXXXVIII, 25 g, 167 mmol) was suspended in POCl₃ (200 mL) and cooled in an ice bath. The mixture was slowly warmed and heated up to 120 °C for 3 h. After this time, the volatiles (excess POCl₃) were evaporated the under vacuum. To this residue was added ice water (200 mL) and the resultant solid was filtered to afford 2-amino-4-
- 20 chloro-7H-pyrrolo[2,3d]pyrimidine (CXXXIX) as a yellow solid (20 g, ~71%, ~75% purity). LCMS (ESI) m/z = 169 (M+H)⁺.

4-Chloro-2-n-propylamino-7H-pyrrolo[2,3d]pyrimidine (CXL)

To a solution of 2-amino-4-chloro-7H-pyrrolo[2,3d]pyrimidine (CXXXIX, 26 g, 155 mmol) and *n*-propionaldehyde (27 g, 464 mmol) in MeOH (600 mL) was added AcOH (50 mL). The reaction was stirred at ambient temperature for 30 min. After this time, NaBH₃CN (49 g, 775 mmol) was added in portions at -20 °C for 30 min. The resultant mixture was stirred at 80 °C for 3 h and the volatiles were removed. The resultant residue was extracted with EtOAc (3 x 300 mL) and the combined organics were washed with a brine solution (2 x 100 mL). The organic layer was dried over Na₂SO₄, concentrated and purified via silica-gel column chromatography (pet ether/EtOAc (5/1)) to afford 4-chloro-2-*n*-propylamino-7H-pyrrolo[2,3d]pyrimidine (CXL) as a yellow solid (6 g, 18%). LCMS (ESI) *m/z* = 211 (M+H)⁺.

N-(2-Propylamino-7H-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine (CXLI)

To a solution of 4-chloro-2-*n*-propylamino-7H-pyrrolo[2,3d]pyrimidine (CXL, 1.0 g, 4.8 mmol) in *n*-BuOH (5 mL) was added potassium carbonate (3.3 g, 5.0 eq.) and *N,O*-dimethylhydroxylamine hydrochloride (1.1 g, 4.0 eq.). The mixture was stirred in an autoclave equipped with a stirrer at 100°C for 8 h. After cooling to ambient temperature, water was added (20 mL) and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with water and then with a brine solution, and dried over anhydrous Na₂SO₄. The solvents were removed in vacuo and the resultant residue was purified by flash column chromatography (pet ether/EtOAc=5/1) to yield *N*-(2-*n*-propylamino-7H-pyrrolo[2,3d]pyrimidin-4-yl)-*N,O*-dimethyl-hydroxylamine (CXLI, 500 mg, 45%).

N-(2-Propylamino-7H-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CXLII)

N-(2-*n*-propylamino-7H-pyrrolo[2,3d]pyrimidin-4-yl)-*N,O*-dimethyl-hydroxylamine (CXLI, 500 mg, 2.1 mmol) was dissolved in H₂O (10 mL) and 0.5 M aqueous HCl solution (5 mL). The solution was then lyophilized to yield *N*-(2-*n*-propylamino-7H-pyrrolo[2,3d]pyrimidin-4-yl)-*N,O*-dimethyl-hydroxylamine

hydrochloride as a white solid (CXLII, 550 mg). LCMS (ESI) $m/z = 236 (M+H)^+$.
 ^1H NMR (500 MHz, MeOD) δ (ppm) 6.74 (d, $J = 3.5$ Hz, 1H), 6.41 (d, $J = 4.0$ Hz, 1H), 3.80 (s, 3H), 3.35 (s, 3H), 3.28-3.35 (m, 2H), 1.59-1.62 (m, 2H), 0.97 (t, $J = 7.0$ Hz, 3H).

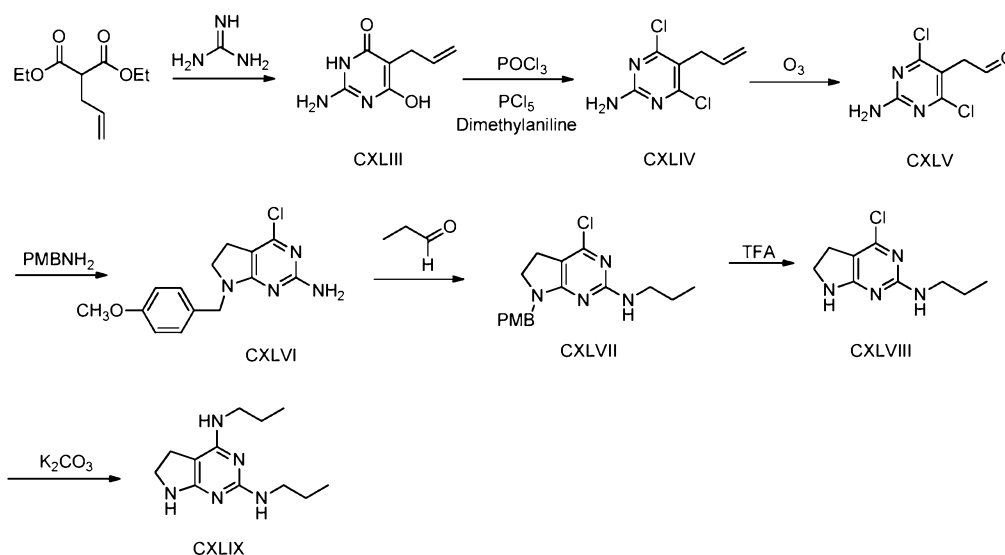
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Example 75: 2,4-Bis-(*n*-propyl)amino-7H-pyrrolidino[2,3-d]pyrimidine (CXLIX)

Example 76: 2,4-Bis-(*n*-propyl)amino-7H-pyrrolidino[2,3-d]pyrimidine hydrochloride (CL)

10 5-Allyl-2-amino-4,6-dihydroxypyrimidine (CXLIII)

Guanidine hydrochloride (27 g, 0.28 mol) was added to cold absolute EtOH (200 mL) and NaOEt (30% in ethanol) (200 mL), and the mixture was stirred at 0 °C for 10 min. After this time, diethyl allylmalonate (55 g, 0.28 mol) was added. The reaction mixture was then stirred at room temperature for 18 h. Acidification with 3N HCl precipitated the crude product (pH=6). The solid was collected by
 15 filtration and washed with ethanol. Recrystallization from water afforded 29 g (62 %) of pure 5-allyl-2-amino-4,6-dihydroxypyrimidine (CXLIII). LCMS (ESI) $m/z = 168 (M+H)^+$.



20

Scheme 51

5-Allyl-2-amino-4,6-chloropyrimidine (CXLIV)

5-Allyl-2-amino-4,6-dihydropyrimidine (4.9 g, 28.0 mmol) was added in small portions to a solution of PCl_5 (6.6 g, 29.5 mmol) in POCl_3 (180 mL) at 60°C , and diethylaniline (3 g) was added dropwise. The temperature was raised to 120°C . The reaction mixture was heated at reflux overnight before it was evaporated to dryness. Hot water (100°C) (100 mL) was added slowly to the residue, and the resulting suspension was cooled and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with cold water three times until the aqueous extract was above pH=5. The organic layer was dried (Na_2SO_4) and evaporated to dryness in vacuo. The resultant residue was purified by column chromatography (EtOAc/pet ether=1:10) to afford 5-allyl-2-amino-4,6-chloropyrimidine (CXLIV, 2.5 g, 42%). LCMS (ESI) $m/z = 204$ ($\text{M}+\text{H}$)⁺.

2-(2-Amino-4,6-chloropyrimidin-5-yl)ethanal (CXLV)

5-Allyl-2-amino-4,6-chloropyrimidine (1 g, 4.9 mmol) was dissolved in ethyl acetate (40 mL) and reacted with ozone gas at -78°C for about 1 h (about 5% ozone at a rate of 1 L/min). The reaction was monitored by TLC (pet ether/AcOEt=3/1 (v/v)), and once the starting material was consumed, the reaction mixture was flushed with oxygen for 10 min. At this time, NaI (3 g) and glacial acetic acid (3 mL) were added simultaneously to the cold reaction mixture, and the temperature was allowed to warm up to 20°C with continuous stirring over a 60-min period. Sodium thiosulfate solution (67 g/100 mL of H_2O) was added to the reaction mixture until it became colorless. The resulting mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (4 x 70 mL). The combined organic extracts were washed successively with H_2O (4 x 30 mL), a saturated NaHCO_3 solution (30 mL) and with a brine solution (30 mL) and lastly, dried over anhydrous Na_2SO_4 . After filtration and evaporation, 2-(2-amino-4,6-chloropyrimidin-5-yl)ethanal (CXLV, 1.1 g, 87%) was isolated as a white solid with ~80% purity. LCMS (ESI) $m/z = 207$ ($\text{M}+\text{H}$)⁺.

2-Amino-4-chloro-7-(4-methoxy)benzyl-pyrrolidino[2,3-d]pyrimidine (CXLVI)

A solution of 2-(2-amino-4,6-chloropyrimidin-5-yl)ethanal (CXLV, 1.2 g, 5.8 mmol) and *para*-methoxybenzylamine (PMBNH_2) (1.6 g, 11.6 mmol) in THF (20 mL) and AcOH (2 mL) was stirred at ambient temperature for 30 min. To this mixture was added $\text{NaBH}(\text{OAc})_3$ (6.2 g, 29 mmol) in portions and the reaction

was stirred overnight. The mixture was concentrated in vacuo, and extracted with EtOAc (3 x 80 mL). The combined organic extracts were then washed with a brine solution (2 x 50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The resultant residue was purified by flash column chromatography (pet ether/EtOAc=10/1) to afford 2-amino-4-chloro-7-(4-methoxy)benzyl-pyrrolidino[2,3-d]pyrimidine (CXLVI, 950 mg, 52%) as a yellow solid (52%). LCMS (ESI) m/z = 291 (M+H)⁺.

10 *2-n-Propylamino-4-chloro-7-(4-methoxy)benzyl-pyrrolidino[2,3-d]pyrimidine (CXLVII)*

2-Amino-4-chloro-7-(4-methoxy)benzyl-pyrrolidino[2,3-d]pyrimidine (CXLVI, 950 mg, 3.3 mmol) and propionaldehyde (575 mg, 16.5 mmol) in MeOH (30 mL) and AcOH (3 mL) were stirred at ambient temperature for 30 min. At this time, NaBH₃CN (1.0 g, 16.5 mmol) was added in portions and the reaction was then heated at 85 °C for 16 h. After cooling, the mixture was evaporated, and extracted with EtOAc (2 x 50 mL). The combined organics were then washed with a brine solution (2 x 50 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The resultant residue was purified by flash column chromatography (PE/EtOAc=10/1) to afford 2-n-propylamino-4-chloro-7-(4-methoxy)benzyl-pyrrolidino[2,3-d]pyrimidine (CXLVII, 920 mg, 85%). LCMS (ESI) m/z = 333 (M+H)⁺.

2-n-Propylamino-4-chloro-7H-pyrrolidino[2,3-d]pyrimidine (CXLVIII)

A solution of 2-n-propylamino-4-chloro-7-(4-methoxy)benzyl-pyrrolidino[2,3-d]pyrimidine (CXLVII, 920 mg, 3.2 mmol) in TFA (5 mL) was heated at 85 °C for 3 h. After cooling the mixture was evaporated and extracted with EtOAc (2 x 50 mL). The combined organics were washed with a brine solution (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The resultant residue was purified by flash column chromatography (pet ether/EtOAc=5/1) to afford 2-n-propylamino-4-chloro-7H-pyrrolidino[2,3-d]pyrimidine (CXLVIII, 500 mg, 85%) as a colorless solid. LCMS (ESI) m/z = 213 (M+H)⁺.

2,4-Bis-(n-propyl)amino-7H-pyrrolidino[2,3-d]pyrimidine (CXLIX)

2-*n*-Propylamino-4-chloro-7H-pyrrolidino[2,3-*d*]pyrimidine (CXLVIII, 500 mg, 2.38 mmol) was dissolved in *n*-butanol (5 mL), and potassium carbonate (1.64 g, 5.0 eq.) and propan-1-amine (923 mg, 4.0 eq.) were added. The mixture was stirred in an autoclave equipped with a stirrer at 100°C for 72 h. After cooling to room temperature, 20 mL of water was added, and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water and with a brine solution, and dried over anhydrous Na₂SO₄. After removal of the solvents in vacuo, the resultant residue was purified by preparative HPLC to yield 2-*n*-propylamino-4-chloro-7H-pyrrolidino[2,3-*d*]pyrimidine (CXLIX, 210 mg, 37% yield).

*2,4-Bis-(n-propyl)amino-7H-pyrrolidino[2,3-*d*]pyrimidine hydrochloride (CL)*

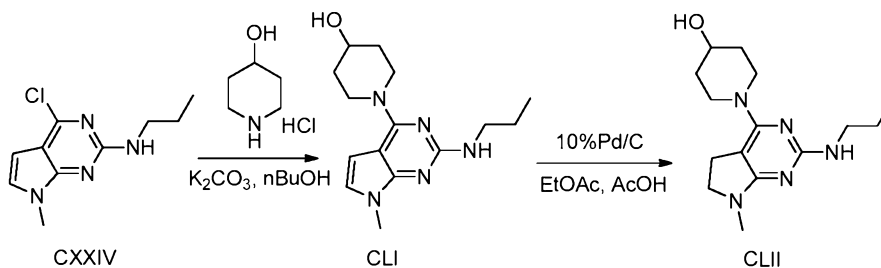
2-*n*-Propylamino-4-chloro-7H-pyrrolidino[2,3-*d*]pyrimidine (CXLIX, 210 mg, 0.89 mmol) was dissolved in H₂O (5 mL) and 0.5 M aqueous HCl solution (2.0 mL), and the solution was lyophilized to yield 2,4-bis-(*n*-propyl)amino-7H-pyrrolidino[2,3-*d*]pyrimidine hydrochloride (CL, 242 mg, 95% yield) as an orange solid. LCMS (ESI) *m/z* = 236 (M+H)⁺. ¹H NMR (500 MHz, MeOD) δ (ppm) 3.72 (t, *J* = 9.0 Hz, 2H), 3.30-3.34 (m, 4H), 2.90 (t, *J* = 9.0 Hz, 2H), 1.61-1.65 (m, 4H), 0.96-0.99 (m, 6H).

Example 77:

2-(*n*-Propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-methyl-pyrrolidino[2,3-*d*]pyrimidine (CLII)

Example 78:

2-(*n*-Propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-methyl-pyrrolidino[2,3-*d*]pyrimidine hydrochloride (CLIII)



Scheme 52

2-(n-Propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-methyl-pyrrolo[2,3-d]pyrimidine (CLI)

2-(*n*-Propyl)amino-4-chloro-7-methyl-pyrrolo[2,3-d]pyrimidine (CXXIV) (1.6 g, 7.1 mmol) was added to *n*-butanol (10 mL) followed by potassium carbonate (4.9 g, 35.5 mmol) and piperidin-4-ol hydrochloride (632 mg, 10.7 mmol).
5 The mixture was stirred in an autoclave equipped with a stirrer at 130 °C for 16 h. After cooling to room temperature, water was added (20 mL), and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water and then with a brine solution, and dried over anhydrous Na₂SO₄. The solvents
10 were removed in vacuo and the residue was purified by flash column chromatography (pet ether/EtOAc=3/1) to yield 2-(*n*-propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-methyl-pyrrolo[2,3-d]pyrimidine (1.2 g, 75%) as a yellow solid. LCMS (ESI) *m/z* = 290 (M+H)⁺.

15 *2-(n-Propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-methyl-pyrrolidino[2,3-d]pyrimidine (CLII)*

To the solution of 2-(*n*-propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-methyl-pyrrolo[2,3-d]pyrimidine (CLI, 1.0 g, 4 mmol) in EtOAc (50 mL) were added 10% Pd/C (1.0 g) and AcOH (2.43 g, 40 mmol). The mixture was attached to a
20 hydrogenation apparatus. The system was evacuated and refilled with hydrogen gas. The mixture was stirred at ambient temperature for 48 h. The mixture was filtered through 10 g of silica-gel on a glass-filter. The filtrate was concentrated and the residue was purified by flash column chromatography (DCM/MeOH=50/1 to 10/1) to yield 2-(*n*-propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-methyl-pyrrolidino[2,3-
25 d]pyrimidine (CLII, 500 mg, 50 % yield) as a yellow solid.

2-(n-Propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-methyl-pyrrolidino[2,3-d]pyrimidine hydrochloride (CLIII)

2-(*n*-Propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-methyl-pyrrolidino[2,3-d]pyrimidine (CLII, 500 mg, 2 mmol) was dissolved in H₂O (10 mL) and 0.5 M HCl solution in H₂O (4 mL) and the solution was lyophilized to yield 2-(*n*-propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-methyl-pyrrolidino[2,3-d]pyrimidine hydrochloride (525 mg) as a yellow solid. LCMS (ESI) *m/z* = 292 (M+H)⁺. ¹H NMR (500 MHz, MeOD) δ (ppm) 4.12-4.15 (m, 2H), 3.80-3.82 (m, 1H), 3.40 (t, *J* = 8.0 Hz,

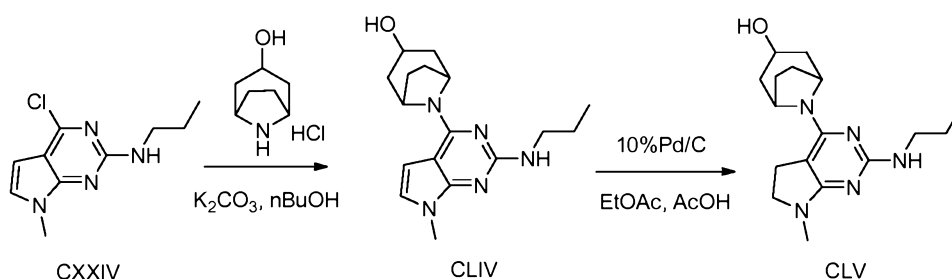
2H), 3.29 (t, $J = 7.0$ Hz, 2H), 3.08-3.14 (m, 2H), 3.02 (t, $J = 8.0$ Hz, 2H), 2.84 (s, 3H), 1.86-1.90 (m, 2H), 1.58-1.62 (m, 2H), 1.46-1.51 (m, 2H), 0.97 (t, $J = 4.0$ Hz, 3H).

5 Example 79:

8-(7-methyl-2-(*n*-propylamino)-pyrrolidino[2,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol (CLV)

Example 80:

10 8-(7-methyl-2-(*n*-propylamino)-pyrrolidino[2,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol hydrochloride (CLVI)



Scheme 53

15 8-(7-Methyl-2-(*n*-propylamino)-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol (CLIV)

To a solution of 2-(*n*-propyl)amino-4-chloro-7-methyl-pyrrolo[2,3-*d*]pyrimidine (CXXIV) (1.0 g, 4.5 mmol) in *n*-butanol (10 mL) were added DIPEA (1.0 g, 7.8 mmol) and 8-aza-bicyclo[3.2.1]octan-3-ol hydrochloride (1.1 g, 6.7 mmol). The mixture was stirred at 125 °C for 16 h. After cooling to room temperature, water (20 mL) was added, and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water and then with a brine solution, and dried over anhydrous Na₂SO₄. The solvents were removed in vacuo and the resultant residue was purified by flash column chromatography (pet ether/EtOAc=6/1) to yield 8-(7-methyl-2-(*n*-propylamino)-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol (CLIV) (800 mg, 57% yield) as a yellow solid. LCMS (ESI) $m/z = 316$ ($M+H$)⁺.

8-(7-Methyl-2-(*n*-propylamino)-pyrrolidino[2,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol (CLV)

To a solution of 2-(*n*-propyl)amino-4-(4-hydroxy-1-azabicyclo[3.2.1]octan-1-yl)-7-methyl-pyrrolo[2,3-*d*]pyrimidine (CLIV, 1.00 g, 3.2 mmol) in EtOAc (10 mL) were added 10% Pd/C (1.0 g) and AcOH (3 mL). The mixture was attached to a hydrogenation apparatus. The system was evacuated and
5 refilled with hydrogen. The mixture was stirred at ambient temperature for 48 h. The mixture was filtered through 10 g of silica-gel on a glass-filter. The filtrate was concentrated and the residue was purified by flash column chromatography (EtOAc/MeOH=50/1) to yield 8-(7-methyl-2-(*n*-propylamino)-pyrrolidino[2,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol (CLV) (500 mg, 49% yield) as a
10 yellow solid.

8-(7-Methyl-2-(n-propylamino)-pyrrolidino[2,3-d]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol hydrochloride (CLVI)

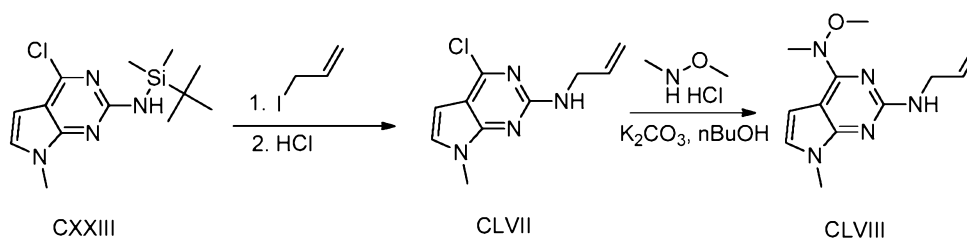
8-(7-Methyl-2-(*n*-propylamino)-pyrrolidino[2,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol (CLV, 200 mg, 0.63 mmol) was dissolved in H₂O (10 mL) and 0.5 M aqueous HCl solution (1.3 mL), and the solution was lyophilized to yield 8-(7-methyl-2-(*n*-propylamino)-pyrrolidino[2,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol hydrochloride (CLVI) (224 mg) as a yellow solid. LCMS (ESI) *m/z* = 318 (M+H)⁺. ¹H NMR (500 MHz, DMSO) δ (ppm) 4.55 (br, 2H), 3.90
15 (s, 1H), 3.60 (t, *J* = 8.0 Hz, 2H), 3.27 (t, *J* = 6.5 Hz, 2 H), 3.00 (t, *J* = 9.0 Hz, 2H), 2.92 (s, 3H), 2.27 (d, *J* = 7.0 Hz, 2H), 1.90-1.95 (m, 4H), 1.69 (s, 1H), 1.66 (s, 1H), 1.49-1.54 (m, 2H), 0.92 (t, *J* = 7.0 Hz, 3H).
20

Example 81:

25 N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine (CLVIII)

Example 82:

N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CLIX)



Scheme 54

2-(Propen-2-yl)amino-4-chloro-7-methyl-pyrrolo[2,3-d]pyrimidine (CLVII)

5 Under a nitrogen atmosphere, 2-(*t*-butyl-dimethylsilyl)amino-4-chloro-7-methyl-pyrrolo[2,3-d]pyrimidine (CXXIII) (7.5 g, 25 mmol) was dissolved in DMF (100 mL) and 3-iodoprop-1-ene (6.38 g, 38 mmol) was added. The mixture was cooled to 0 °C with vigorous stirring, then NaH (1.5 g of a 60% dispersion in mineral oil, 38 mmol) was added. The mixture was stirred for 30 min, and water (50

10 mL) was slowly added to quench the reaction. The aqueous mixture was extracted with EtOAc (300 mL) and the organic layer was washed with water (100 mL) and then with a brine solution (100 mL), and dried over anhydrous Na₂SO₄. After evaporation, 8.6 g of a yellow oily residue was isolated. This material was dissolved in Et₂O (100 mL), and concentrated hydrochloric acid (20 mL) was added at 0 °C with

15 stirring. The mixture was then stirred for an additional 10 min. The mixture was extracted with EtOAc (200 mL) and 1N NaOH (200 mL). The organic layer was separated and washed with H₂O (150 mL) and with a brine solution (150 mL) and dried over anhydrous Na₂SO₄. The solvents were removed in vacuo and the resultant residue was purified by flash column chromatography (pet ether/EtOAc=10/1 to 5/1)

20 to yield 2-(propen-2-yl)amino-4-chloro-7-methyl-pyrrolo[2,3-d]pyrimidine (6 g, 100% yield) as a yellow solid. LCMS: (ESI) *m/z* = 223 (M+H)⁺.

N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3-d]pyrimidin-4-yl)-N,O-dimethylhydroxylamine (CLVIII)

25 To 2-(propen-2-yl)amino-4-chloro-7-methyl-pyrrolo[2,3-d]pyrimidine (CLVII, 500 mg, 2.38 mmol) were added *n*-butanol (5 mL), potassium carbonate (1.64 g, 5.0 eq.) and N,O-dimethylhydroxylamine hydrochloride (923 mg, 4.0 eq.). The mixture was stirred in an autoclave equipped with a stirrer at 100 °C for 8 h. After cooling to room temperature, water (20 mL) was added, and the mixture was

30 extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with

water and with a brine solution and dried over anhydrous Na₂SO₄. The solvents were then removed in vacuo and the resultant residue was purified by flash column chromatography (pet ether/EtOAc=3/1) to yield N-(2-(propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine (CLVIII, 310 mg, 55% yield).

N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CLIX)

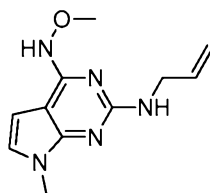
N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine (310 mg, 1.32 mmol) was dissolved in H₂O (5 mL) and 0.5 M aqueous HCl solution (2.7 mL), and the solution was lyophilized to yield N-(2-(propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CLIX, 325 mg) as a white solid. LCMS (ESI) m/z = 248 (M+H)⁺. ¹H NMR (500 MHz, DMSO) δ (ppm) 12.60- 14.80 (br, 1H), 7.70-8.70 (br, 1H), 7.06 (s, 1H), 6.55 (s, 1H), 5.90-5.94 (m, 1H), 5.31 (d, *J* = 17.0 Hz, 1H), 5.17 (d, *J* = 10.5 Hz, 1H), 4.06 (s, 2H), 3.84 (s, 3H), 3.70 (s, 3H), 3.53 (s, 3H).

Example 83:

N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine (CLX)

Example 84:

N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine hydrochloride (CLXI)



CLX

Scheme 55

N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine (CLX)

2-(2-Propen-2-yl)amino-4-chloro-7-methyl-pyrrolo[2,3-d]pyrimidine (CLVII) (700 mg, 3.15 mmol) was dissolved in *n*-butanol, and potassium carbonate (2.2 g, 5.0 eq.) and O-methylhydroxylamine hydrochloride (768 mg, 4.0 eq.) were

added. The mixture was stirred in an autoclave equipped with a stirrer at 100 °C for 12 h. After cooling to room temperature, water (20 mL) was added, and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with water and a brine solution, and dried over anhydrous Na₂SO₄. The solvents were removed in vacuo and the resultant residue was purified by flash column chromatography (pet ether/EtOAc=5/1) to yield N-(2-(propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine (370 mg, 46% yield).

N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine hydrochloride (CLXI)

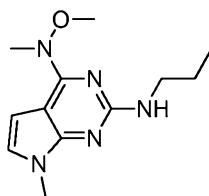
N-(2-(propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine (370 mg, 1.59mmol) was dissolved in H₂O (5 mL) and 0.5 M aqueous HCl solution (2 mL), and the solution was lyophilized to yield N-(2-(propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine hydrochloride (383 mg) as a white solid. LCMS (ESI) m/z = 234 (M+H)⁺. ¹H NMR (500 MHz, DMSO) δ (ppm) 12.40-13.00 (br, 1H), 7.70-8.10 (br, 1H), 7.04 (d, *J* = 3.5 Hz, 1H), 6.49 (d, *J* = 3.0 Hz, 1H), 5.94-5.99 (m, 1H), 5.32 (d, *J* = 17.0 Hz, 1H), 5.17 (d, *J* = 10.5 Hz, 1H), 4.04 (s, 2H), 3.85 (s, 3H), 3.61 (s, 3H).

Example 85:

N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine (CLXII)

Example 86:

N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine hydrochloride (CLXIII)



CLXII

Scheme 56

N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine (CLXII)

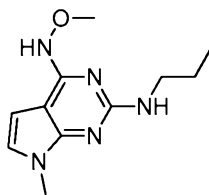
The desired compound was prepared from 4-chloro-2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidine and N,O-dimethyl-hydroxylamine as described in Example 73. LCMS: (ESI) $m/z = 250$ (M+H)⁺. ¹H NMR (500 MHz, CDCl₃) δ (ppm) 7.70 (s, 1H), 7.02 (s, 1H), 6.52 (s, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.53 (s, 3H), 3.34 (t, $J=8.5$ Hz, 2H), 1.54-1.59 (m, 2H), 0.93 (t, $J=8.5$ Hz, 3H).

Example 87:

N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine (CLXIV)

10 Example 88:

N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine hydrochloride (CLXV)



CLXIV

Scheme 57

15 N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine (CLXIV)

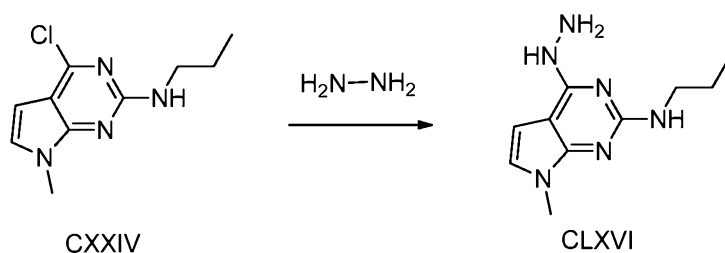
The desired compound was prepared from 4-chloro-2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidine and O-methyl-hydroxylamine as described in Example 73. LCMS (ESI) $m/z = 236$ (M+H)⁺. ¹H NMR (500 MHz, DMSO) δ (ppm) 12.50 (s, 1H), 8.10 (s, 1H), 7.05 (s, 1H), 6.01 (s, 1H), 3.85 (s, 3H), 3.60 (s, 3H), 3.36 (s, 1H), 3.34 (t, $J = 6.5$ Hz, 2H), 1.58-1.62 (m, 2H), 0.96 (t, $J = 7.5$ Hz, 3H).

Example 89:

N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine (CLXVI)

25 Example 90:

N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine hydrochloride (CLXVII)



Scheme 58

N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine (CLXVI)

To a solution of 4-chloro-2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidine (CXXIV, 1.0 g, 4.5 mmol) in ethanol (70 mL) was added hydrazine (14 mL) and the mixture was heated at reflux for 3 h. After cooling to room temperature, the solvents were removed in vacuo. The residue was purified by flash column chromatography (CH₂Cl₂/MeOH=30/1) to yield *N*-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine (CLXVI, 1.0 g, 80% yield).

10

N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine hydrochloride (CLXVII)

N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine (460 mg, 2.0 mmol) was dissolved in H₂O (10 mL) and 0.5 M aqueous HCl solution (4 mL), and the solution was lyophilized to yield *N*-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine hydrochloride (440 mg) as a brown solid. LCMS (ESI) *m/z* = 221 (M+H)⁺. ¹H NMR (500 MHz, DMSO) δ (ppm) 10.63 (s, 1H), 7.56 (s, 2H), 6.97 (d, *J* = 3.0 Hz, 1H), 6.54 (d, *J* = 3.5 Hz, 1H), 3.58 (s, 3H), 3.33 (s, 2H), 1.56-1.61 (m, 2H), 0.95 (t, *J* = 8.0 Hz, 3H).

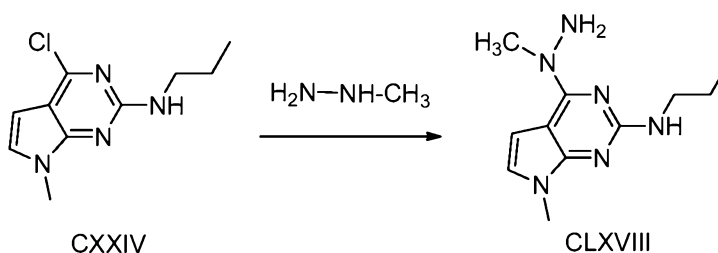
20

Example 91:

N-Methyl-*N*-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine (CLXVIII)

Example 92:

25 *N*-Methyl-*N*-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine hydrochloride (CLXIX)



Scheme 59

N-Methyl-N-(2-n-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine (CLXVIII)

5 To a solution of 4-chloro-2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidine (CXXIV, 800 mg, 3.42 mmol) in *n*-butanol (5 mL) was added potassium carbonate (2.36 g, 5.0 eq.) and methylhydrazine (630 mg, 4.0 eq.). The mixture was stirred in an autoclave equipped with a stirrer at 100 °C for 15 h. After cooling to room temperature, water was added (20 mL), and the mixture was
 10 extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with water and with a brine solution, and dried over anhydrous Na₂SO₄. The solvents were removed in vacuo and the resultant residue was purified by flash column chromatography (pet ether/EtOAc=3/1 to DCM/MeOH=10/1) to yield *N*-methyl-*N*-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine (CLXVIII, 220
 15 mg, 36% yield).

N-Methyl-N-(2-n-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine hydrochloride (CLXIX)

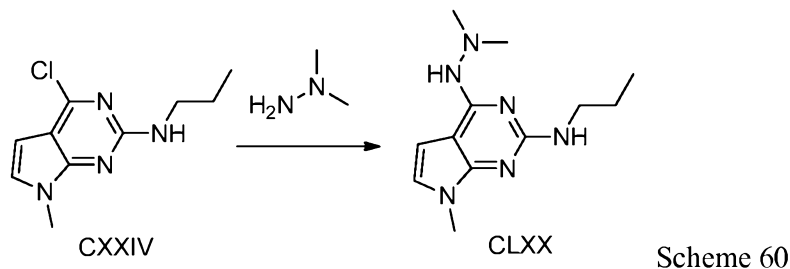
N-methyl-*N*-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-
 20 hydrazine (220 mg, 0.94 mmol) was dissolved in H₂O (10 mL) and 0.5 M aqueous HCl solution (2 mL), and the solution was lyophilized to yield *N*-methyl-*N*-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine hydrochloride (CLXIX, 238 mg) as a brown solid. LCMS (ESI) *m/z* = 235 (M+H)⁺. ¹H NMR (500 MHz, DMSO) δ (ppm) 7.50-8.10 (br, 4H), 7.05 (s, 1H), 6.67 (s, 1H), 3.60 (s, 3H),
 25 3.58 (s, 3H), 3.33 (s, 2H), 1.55-1.62 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H).

Example 93:

N,N-Dimethyl-*N'*-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine (CLXX)

Example 94:

N,N-Dimethyl-N'-(2-n-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine hydrochloride (CLXXI)



5

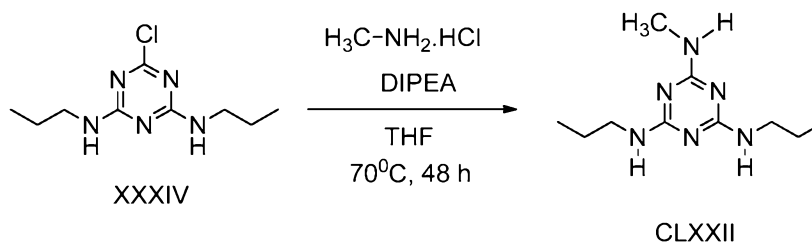
N,N-Dimethyl-N'-(2-n-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine (CLXX)

To a solution of 4-chloro-2-n-propylamino-7-methyl-pyrrolo[2,3d]-pyrimidine (1.1 g, 5 mmol) and 1,1-dimethylhydrazine (450 mg, 7.5 mmol) in dioxane (30 mL) was added xphos (622 mg, 1 mmol), Pd₂(dba)₃ (458 mg, 0.5 mmol) and Cs₂CO₃ (2.45 g, 7.5 mmol). The solution was degassed by bubbling argon through it for 10 min using a syringe needle. The mixture was then stirred at 80 °C for 2 h. After cooling to room temperature, water was added (20 mL) and the mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with water and with a brine solution, and dried over anhydrous Na₂SO₄. The solvents were removed in vacuo and the resultant residue was purified by flash column chromatography (DCM/MeOH=30/1 to 5/1) to yield N, N-dimethyl-N'-(2-n-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine (CLXX, 100 mg, 8% yield, ~85% purity).

20

N,N-Dimethyl-N'-(2-n-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine hydrochloride (CLXXI)

N, N-dimethyl-N'-(2-n-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine (100 mg, 0.4 mmol) was dissolved in H₂O (5 mL) and 0.5 M aqueous HCl solution (1 mL) and the solution was lyophilized to yield N, N-dimethyl-N'-(2-n-propylamino-7-methyl-pyrrolo[2,3-d]pyrimidin-4-yl)-hydrazine hydrochloride (110 mg) as a yellow oil. LCMS (ESI) m/z = 249 (M+H)⁺. ¹H NMR (500 MHz, MeOD) δ (ppm) 6.92 (d, J = 4.0 Hz, 1H), 6.50 (d, J = 3.0 Hz, 1H), 3.66 (s, 3H), 3.45 (t, J = 7.5 Hz, 2H), 2.79 (s, 6H), 1.67-1.72 (m, 2H), 1.01-1.04 (m, 3H).

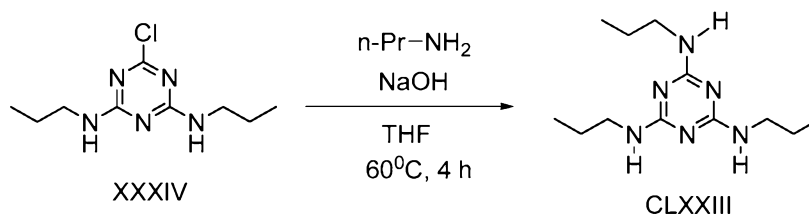
Example 95:N-(2,4-Bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine (CLXXII)

5

Scheme 61

A pressure tube was charged with 2-chloro-N-(4,6-bis-(*n*-propylamino)-[1,3,5-triazine (XXXIV) (1.50 g, 6.53 mmol), N,N-diisopropylethylamine (5.4 mL, 32.65 mmol), methylamine hydrochloride (2.2 g, 32.65 mmol) and tetrahydrofuran (20 mL). The reaction mixture was heated at 70 °C for 48 h. An additional amount of N,N-diisopropylethylamine (5.4 mL, 32.65 mmol) and methylamine hydrochloride (2.2 g, 32.65 mmol) were added, and the reaction mixture was heated at 70 °C for an additional 48 h. The mixture was poured into saturated NaHCO₃ solution (40 mL). The suspension was extracted with EtOAc (3 x 70 mL). The combined organic extracts were washed with water (70 mL), then with a brine solution (70 mL) and lastly dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using gradient elution from petroleum ether/EtOAc (9:1, (v/v)) to petroleum ether/EtOAc (1:4, (v/v)) to yield N-(2,4-bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine (0.35 g, 24%). 400 MHz ¹H NMR (DMSO-*d*₆, ppm) 6.69-6.02 (3H, m), 3.22-3.02 (4H, m), 2.68 (3H, s), 1.55-1.38 (4H, m), 0.84 (6H, t, J=7.4 Hz). ESI-MS (m/z): 225 [M+H]⁺.

Example 96:25 N-(2,4,6-Tris-*n*-propylamino)-[1,3,5]triazine (CLXXIII)Example 97:N-(2,4,6-Tris-*n*-propylamino)-[1,3,5]triazine hydrogen sulfate (CLXXIV)



Scheme 62

N-(2,4,6-Tris-*n*-propylamino)-[1,3,5]triazine (CLXXIII)

- 5 A mixture of 2-chloro-*N*-(4,6-bis-(*n*-propylamino)-[1,3,5]triazine (XXXIV) (1.00 g, 4.35 mmol), NaOH (348 mg, 8.70 mmol) and *n*-propylamine (1.4 mL, 17.40 mmol) in 1,4-dioxane (40 mL) was heated at 60 °C for 4 h. The volatiles were then removed under reduced pressure. Water (50 mL) was added to the residue and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic
- 10 extracts were washed with water (50 mL), then with a brine solution (50 mL) and lastly, dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography using gradient elution from CH₂Cl₂/EtOH (99:1, (v/v)) to CH₂Cl₂/EtOH (97:3 (v/v)) to yield *N*-(2,4,6-tris-*n*-propylamino)-[1,3,5]triazine (790 mg, 72%). 400 MHz ¹H-NMR
- 15 (CDCl₃, ppm) 4.93-4.51 (3H, br s), 3.41-3.22 (6H, m), 1.62-1.49 (6H, m), 0.94 (9H, t, J=7.4 Hz). ESI-MS (m/z): 253 [M+H]⁺.

N-(2,4,6-Tris-*n*-propylamino)-[1,3,5]triazine hydrogen sulfate (CLXXIV)

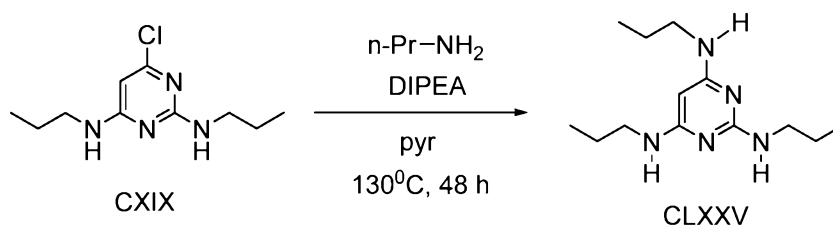
- The title compound was prepared from *N*-(2,4,6-tris-*n*-propylamino)-[1,3,5]triazine and 95% H₂SO₄ in quantitative yield, as described in Example 8A. 400
- 20 MHz ¹H-NMR (DMSO-d₆, ppm) 8.26 (1H, br s) 8.10-7.99 (1H, m) 7.94-7.85 (1H, m) 3.33-3.16 (6H, m) 1.60-1.45 (6H, m) 0.88 (9H, t, J=7.5 Hz). ESI-MS (m/z): 253 [M+H]⁺.

25 Example 98:

N-(2,4,6-Tris-*n*-propylamino)-1,3-pyrimidine (CLXXV)

Example 99:

N-(2,4,6-Tris-*n*-propylamino)-1,3-pyrimidine hydrogen sulfate (CLXXVI)

Scheme 63*N*-(2,4,6-Tris-*n*-propylamino)-1,3-pyrimidine (CLXXV)

- 5 A pressure tube was charged with 4-chloro-2,6-bis-(*N*-*n*-propylamino)-1,3-pyrimidine (CXIX) (1.53 g, 6.65 mmol), *n*-propylamine (2.7 mL, 33.25 mmol), *N,N*-diisopropylethylamine (2.3 mL, 13.30 mmol) and pyridine (15 mL). The reaction mixture was heated at 130 °C for 48 hours. The volatiles were removed under reduced pressure. Water (50 mL) was added to the residue and the mixture was
- 10 extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were washed with water (100 mL) and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography using gradient elution from CH₂Cl₂/EtOH (99:1, (v/v)) to CH₂Cl₂/EtOH (95:5, (v/v)) to yield *N*-(2,4,6-tris-*n*-propylamino)-1,3-pyrimidine (0.90 g, 54%). 400 MHz ¹H NMR
- 15 (DMSO-*d*₆, ppm) 5.43 (1H, br s), 5.15 (1H, br s), 4.74 (1H, s), 3.27 (2H, td, *J*=6.9, 5.9 Hz), 3.16-3.09 (4H, m), 1.65-1.51 (6H, m), 0.96 (6H, t, *J*=7.4 Hz), 0.93 (3H, t, *J*=7.3 Hz). ESI-MS (*m/z*): 252 [M+H]⁺.

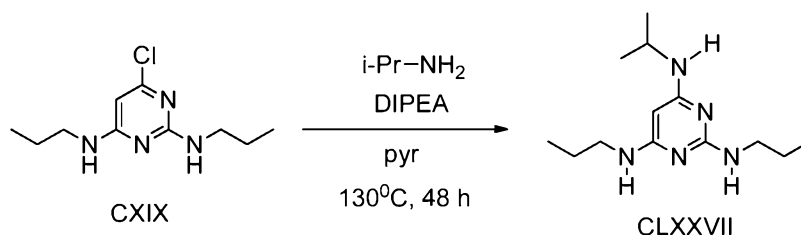
N-(2,4,6-Tris-*n*-propylamino)-1,3-pyrimidine hydrogen sulfate (CLXXVI)

- 20 The title compound was prepared from *N*-(2,4,6-tris-*n*-propylamino)-1,3-pyrimidine and 95% H₂SO₄ in quantitative yield, as described in Example 8A. 400 MHz ¹H-NMR (DMSO-*d*₆, ppm) 10.81-10.58 (1H, br s) 7.9-7.7 (1H, m) 7.6-6.5 (3H, m) 5.01 (1H, s) 3.30-3.12 (4H, m) 3.09-2.94 (2H, m) 1.59-1.46 (6H, m) 0.94-0.84 (9H, m). ESI-MS (*m/z*): 252 [M+H]⁺.

25

Example 100:*N*-(4-*i*-Propylamino)-*N*-(2,6-bis-*n*-propylamino)-1,3-pyrimidine (CLXXVII)Example 101:

N-(4-*i*-Propylamino)-N-(2,6-bis-*n*-propylamino)-1,3-pyrimidine hydrogen sulfate (CLXXVIII)



Scheme 64

5

N-(4-*i*-Propylamino)-*N*-(2,6-bis-*n*-propylamino)-1,3-pyrimidine (CLXXVII)

The title compound was prepared from 4-chloro-2,6-bis-(*N*-*n*-propylamino)-1,3-pyrimidine (CXIX) and *i*-propylamine as described in Example 98 in 16% yield. 400 MHz ¹H NMR (DMSO-*d*₆, ppm) 5.78 (1H, br s), 5.46 (1H, br s), 5.19 (1H, br s), 4.73 (1H, s), 3.83-3.71 (1H, m), 3.34-3.27 (2H, m), 3.19-3.10 (2H, m), 1.68-1.53 (4H, m), 1.23 (6H, d, *J*=6.4 Hz), 0.98 (3H, t, *J*=7.4 Hz), 0.94 (3H, t, *J*=7.4 Hz). ESI-MS (*m/z*): 252 [*M*+*H*]⁺.

10

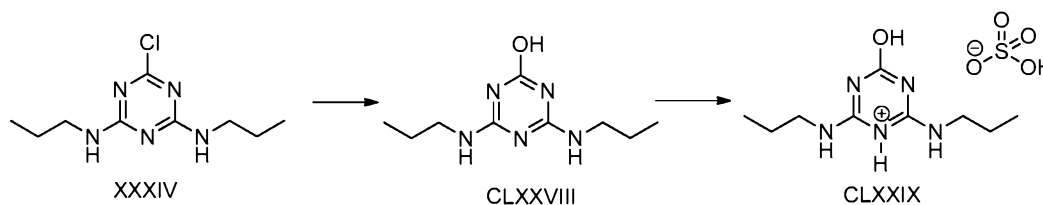
N-(4-*i*-Propylamino)-*N*-(2,6-bis-*n*-propylamino)-1,3-pyrimidine hydrogen sulfate (CLXXVIII)

15

The title compound was prepared from *N*-(4-*i*-propylamino)-*N*-(2,6-bis-*n*-propylamino)-1,3-pyrimidine and 95% H₂SO₄ in quantitative yield, as described in Example 8A. 400 MHz ¹H-NMR (DMSO-*d*₆, ppm) 0.76-10.40 (1H, m), 8.0-7.1(3H, m), 5.01 (1H, s), 4.18-3.93 (1H, m), 3.35-3.13 (3H, m), 3.12-2.94 (1H, m), 1.60-1.45 (4H, m), 1.19-1.11 (6H, m), 0.93-0.83 (6H, m). ESI-MS (*m/z*): 252 [*M*+*H*]⁺.

20

Comparative Example 1:



25

Scheme 65

N-(4,6-Bis(propylamino)-1,3,5-triazin-2-ol (CLXXVIII))

A vial was charged with 6-chloro- N^2,N^4 -dipropyl-1,3,5-triazine-2,4-diamine (XXXIV) (800 mg, 3.48 mmol), NaOH (696 mg, 17.40 mmol), water (3 mL) and 1,4-dioxane (3 mL). The reaction mixture was heated at 140 °C for 30 min under microwave irradiation. The mixture was acidified with 1N HCl to pH 5, precipitate were filtered, washed with water. The product was dissolved in 50% trifluoroacetic acid (30 mL), the indissoluble residue was filtered off. The filtrate was neutralized with saturated NaHCO_3 solution, the formed precipitate was filtered, washed with water, acetone and dried to give 550 mg (75%) of 4,6-bis(propylamino)-1,3,5-triazin-2-ol (CLXXVIII). 400 MHz ^1H NMR ($\text{DMSO}-d_6 + \text{CF}_3\text{COOD}$, ppm) 3.18-3.34 (4H, m), 1.45-1.59 (4H, m), 0.86 (6H, t). ESI-MS (m/z): 212 $[\text{M}+\text{H}]^+$.

N-(4,6-Bis(propylamino)-1,3,5-triazin-2-ol hydrogen sulfate (CLXXIX))

95% H_2SO_4 (28 μL , 0.52 mmol) was added to the suspension of 4,6-bis(propylamino)-1,3,5-triazin-2-ol (CLXXVIII) (110 mg, 0.52 mmol) in 1,4-dioxane (2 mL). The mixture was stirred for 30 min at room temperature. The resultant precipitate were filtered, washed with Et_2O and dried to afford 4,6-bis(propylamino)-1,3,5-triazin-2-ol hydrogen sulfate (CLXXIX) in quantitative yield. 400 MHz ^1H NMR ($\text{CD}_3\text{OD} + \text{CF}_3\text{COOD}$, ppm) 3.35-3.45 (3.2H, m), 3.22-3.27 (0.8H, m), 1.58-1.70 (4H, m), 0.91-1.0 (6H, m). ESI-MS (m/z): 212 $[\text{M}+\text{H}]^+$. Major Fragments ($\text{M}+\text{H}$) 170, 128, 86.

Example 102:

Preparation of (XXXVI) Salt Form A (Figure 1)

Method A:

To (XXXV) in ethyl acetate at ambient temperature (ca. 151 mg/mL, clear solution) was added a solution of one molar equivalent of concentrated sulfuric acid in ethanol. The clear solution was stirred at ambient temperature for ca. 1 day (clear), after which 6 volume equivalents of isopropyl ether (vs. ethyl acetate) were added, resulting in a cloudy mixture. The mixture was stirred for 3 days, then filtered to yield solid product (Hydrogen Sulfate Salt Form A).

Method B:

To (XXXV) in methyl ethyl ketone at ca. 65 °C (ca. 104 mg/mL, clear solution) was added one molar equivalent concentrated sulfuric acid. A precipitate that immediately formed rapidly redissolved. The mixture was stirred at ca. 65 °C for ca. 5 h and slowly cooled over ca. 1 h to ambient temperature. The mixture was stirred for one day at ambient temperature, then filtered to yield solid product (61% yield) (Hydrogen Sulfate Salt Form A).

Method C:

To (XXXV) in methyl ethyl ketone at ca. 65 °C (ca. 100 mg/mL, clear solution) was added one molar equivalent of concentrated sulfuric acid. A precipitate that formed immediately rapidly redissolved. The mixture was stirred at ca. 65 °C for ca. 1 h and slowly cooled over 1 h to ambient temperature, yielding solids in the form of rods. The mixture was stirred for ca. 4 h at ambient temperature. One volume equivalent of heptane (vs. methyl ethyl ketone) was added and the mixture was stirred for 1 day at ambient temperature, then was filtered to collect solid product (81% yield) (Hydrogen Sulfate Salt Form A).

Method D:

To (XXXV) in methyl ethyl ketone at ca. 69 °C (ca. 200 mg/mL, clear solution) was added one molar equivalent of concentrated sulfuric acid. A precipitate that formed immediately rapidly redissolved. The mixture was stirred at ca. 69 °C for ca. 1 h and quickly cooled to ambient temperature and stirred for ca. 0.5 h, yielding a thick paste. The mixture was stirred in an ice bath for ca. 45 minutes, then filtered to collect solid product (Hydrogen Sulfate Salt Form A).

Method E:

To (XXXV) in methyl ethyl ketone at ca. 67 °C (ca. 101 mg/mL, clear solution) was added one molar equivalent of concentrated sulfuric acid. The mixture was stirred at ca. 67 °C for ca. 1 h and slowly cooled to ambient temperature. The mixture was stirred for ca. 1.5 h at ambient temperature, then one volume equivalent (vs. methyl ethyl ketone) of methyl *tert*-butyl ether was added, the mixture was stirred for one day, then filtered to collect solid product (76% yield) (Hydrogen Sulfate Salt Form A).

Method F:

To (XXXV) in acetone at ca. 50 °C (ca. 199 mg/mL, clear solution) was added one molar equivalent of concentrated sulfuric acid, forming a clear solution. The mixture was stirred at ca. 50 °C for ca. 1 h and slowly cooled to ambient

temperature, at which point solids had formed. To the mixture was added about two volume equivalents (vs. methyl ethyl ketone) of methyl *tert*-butyl ether. The mixture was stirred for one day at ambient temperature, then filtered to collect solid product (79% yield) (Hydrogen Sulfate Salt Form A).

5

Example 103:

Preparation of a Mixture of (XXXVI) Salt Form A and (XXXVI) Salt Form B

To (XXXV) in ethyl acetate at ca. 65°C (99 mg/mL, clear solution) was added one molar equivalent of concentrated sulfuric acid. A thick suspension
10 within 5 minutes along with a small amount of tacky material. The mixture was stirred at ca. 65 °C for about 5 h, slowly cooled to ambient temperature, stirred for 4 days then filtered to collect solid product (Hydrogen Sulfate Salt Form A as a Mixture with Form B), Figure 23

15

Example 104:

Preparation of (XXXVI) Salt Form C

A sample of (XXXVI) Form A was exposed to 97% relative humidity at ambient temperature for 4 days. The resulting solid form was designated Hydrogen Sulfate Form C. The resulting material under thermal gravimetric testing lost 4.6
20 wt% between about 30 and 50°C, consistent with approximately one molar equivalent of water (Figure 24).

Example 105:

Preparation of (XXXVI) Salt Form D

25 To (XXXV) in ethyl acetate at ca. 65 °C (ca.100 mg/mL) was added one molar equivalent of concentrated sulfuric acid. Tacky material immediately precipitated and more solids were observed after ca. 5 minutes. A subsample of these solids were removed with a pipette and filtered without cooling. These solid was designated Hydrogen Sulfate Salt Form D (Figure 25).

30

Example 106:

Preparation of a Mixture of (XXXVI) Salt Form A and (XXXVI) Salt Form D

To (XXXV) in isopropyl acetate at ca. 80 °C (203 mg / mL, clear solution) was added one molar equivalent of concentrated sulfuric acid as a solution

in isopropyl acetate. A precipitate formed. The mixture was stirred at ca. 80 °C for ca. 45 minutes, then was slowly cooled to ambient temperature, stirred for day, then filtered to yield the solid product (83% yield); Hydrogen Sulfate Form A in a Mixture with Hydrogen Sulfate Form D (Figure 26).

5

Example 107:

Preparation of N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine Phosphoric Acid Salt (CLXXX), Form A

To (XXXV) in acetonitrile at ambient temperature were added two molar equivalents of phosphoric acid. The mixture was stirred for 2 days, then the solid that was formed was collected by filtration and dried on the filter under a nitrogen stream (Phosphoric Acid Salt Form A; Figure 27).

Example 108:

15 Preparation of (CLXXX) Form C

To (XXXV) in methanol at ambient temperature (clear solution) was added one molar equivalent of phosphoric acid, resulting in a clear solution. The vial containing the solution was placed in an enclosed chamber with a vial of isopropyl ether and vapor diffused, forming a solid which was collected by filtration (Phosphoric Acid Salt Form C, Figure 28).

Example 109:

Preparation of a Mixture of (CLXXX) Form A and (CLXXX) Form B

To (XXXV) in acetonitrile (slurry) at ambient temperature was added one molar equivalent of phosphoric acid. A thick slurry formed. The slurry was sonicated at ambient temperature for 3 days, then was filtered to collect the solid product (Phosphoric Acid Salt Form A in a Mixture with Form B, Figure 29).

Example 110:

30 Preparation of a Mixture of (CLXXX) Form C and (CLXXX) Form D

To (XXXV) in ethyl acetate (clear solution) were added two molar equivalents of phosphoric acid as a solution in ethanol. A precipitate formed. The mixture was further diluted with ethyl acetate, stirred for 3 days, then filtered to

collect solid product (a mixture of Phosphoric Acid Salt Form C and Phosphoric Acid Salt Form D, Figure 30).

Example 111:

5 Preparation of a Mixture of (CLXXX) Form C and (CLXXX) Form E

To (XXXV) in tetrahydrofuran (clear solution) at ambient temperature were added three molar equivalents of phosphoric acid. A precipitate formed. The mixture was stirred at ambient temperature for 3 days, then filtered to collect solid product (a mixture of Phosphoric Acid Salt Form C and Phosphoric Acid Salt Form E,
10 Figure 31).

Example 112:

Effect of Compound (XXXVI) on Opioid-Induced Respiratory Depression in the Rat

Rats with pre-cannulated jugular vein (for administering drugs) were
15 acclimated to plethysmography chambers for a minimum of 60 minutes, or until animals were no longer restless. Each animal was dosed with morphine sulfate (10 mg/kg), dissolved in sterile water at a concentration of 10 mg/mL (supplied by Baxter Healthcare Corporation), via injection into the jugular vein catheter over a period of 5-10 seconds.

20 Compound (XXXVI) was dissolved in 20% hydroxypropyl β -cyclodextran (20%bcd on graph) at a concentration of 0.45 mg/mL at pH 5. After a period of 5 min, compound (XXXVI), labeled as cmpd (A), was administered via infusion into the jugular vein at a dose of 0.10 mg/kg/min for 20 min and then at a dose of 0.30 mg/kg/min for 20 min (e.g., 20 μ L/min/0.3 kg rat to yield 0.03
25 mpk/min).

After 20 minutes of infusion at this dose, the infusion pumps were turned off, and all animals were given a 20 minute recovery period, followed by a post-study analysis of rat health and behavior. The minute ventilation data indicate that compound (XXXVI) significantly reversed opioid-induced respiratory depression
30 in rat compared to vehicle. Results are illustrated in Figure 1.

Example 113:Effects of Morphine and Compound (XXXVI) on Blood Gases in the Rat

Rats with pre-cannulated jugular vein and femoral arterial catheters (for administering drugs and obtaining blood samples respectively) were obtained from Harlan laboratories and kept at the animal facility at Galleon Pharmaceuticals until the experimental procedures. Each animal was dosed with morphine sulfate (10 mg/kg), dissolved in saline at a concentration of 10 mg/mL, via injection into the jugular vein over a period of 20 seconds with a 20 second flush of 0.9% NaCl saline. Prior to morphine administration, two 250 μ L samples of arterial blood were aspirated from the femoral artery into a pre-heparinized syringe. The samples were analyzed on Radiometer's ABL Flex 800, where pO₂, pCO₂, pH, SaO₂ and other parameters were recorded. Aspirated volumes of arterial blood were replaced by room temperature sterile saline (~300 μ L) slowly flushed back into the femoral arterial catheter of the rodent to prevent hypovolemia. Morphine was then administered and 2 minutes later another blood sample was taken.

After a period of 5 min from the administration of morphine, compound (XXXVI), labeled as cmpd (A), was administered via infusion into the jugular vein at a dose of 0.1, 0.3 and 1.0 mg/kg/min (dissolved in PBS buffer). The infusion started at t = 15 minutes and ended at t = 35 minutes. Arterial blood gas analysis occurred at time points t = 12, 18, 25, 35, 40, 45, and 50 minutes. The data show that compound (XXXVI) significantly reverses opioid-induced respiratory depression in rat compared to vehicle. Results are illustrated in Figure 2a and Figure 2b and the accompanying Table 6.

Table 6.

Cmpd	n	Dose (mg/kg/min)	pH (% reversal)	PaCO ₂ (% reversal)	PaO ₂ (% reversal)	SaO ₂ (% reversal)
XXXVI	6	1	60	94	26	62
XXXVI	11	0.3	55	72	-16	43
XXXVI	10	0.1	37	47	16	51
XXXVI	6	0.03	20	18	-2.0	42

25

Example 114:Hypoxic Ventilatory Response (HVR) and Effect of Compound (XXXVI) on HVR in the Rat

Rats with a pre-cannulated jugular vein (for administering drugs) were acclimated to plethysmography chambers for a minimum of 60 minutes, or until animals were no longer restless. Each animal was dosed with compound (XXXVI), labeled as cmpd (A), at 0.03 mg/kg/min via infusion into the jugular vein catheter for a period of 50 minutes. After a period of 20 minutes, an isocapnic hypoxic mixture (12% O₂ balanced N₂) was administered into all chambers using a gas mixer (CWE inc. GSM-3 gas mixer) for 20 minutes. After this time, the gas mixer was turned off, resulting in normal room air pumped into the chambers. Ten minutes later, the infusion pumps were turned off, and all animals were given a 20 minute recovery period, followed by a post-study analysis of rat health and behavior. The minute ventilation data show that compound (XXXVI) significantly potentiates the hypoxic ventilatory response in the rat compared to vehicle. Results are illustrated in Figure 3.

Example 115:Effect of Compound (XXXVI) on Opioid-Induced Respiratory Depression in the Monkey

Juvenile macaques (four-year-old *Macaca fascicularis*, 2 to 5 kg, n=13) were used for the study. Animal husbandry was conducted under USDA guidelines and the protocols were approved by the Institutional Animal Care and Use Committee of East Carolina University.

Anesthesia was induced with 5% isoflurane and then maintained with 1.5 to 2% isoflurane (100% O₂, 2 L/min). Antebrachial veins were cannulated. Vivometrics Lifeshirts (Ventura, CA) were fitted to the animals for monitoring respiratory function by inductance plethysmography. Abdomen and rib cage deflections were calibrated using the Qualitative Diagnostic Calibration (QDC) procedure, and tidal volume was normalized to 15 mL, which represented a typical tidal volume for these animals as previously measured using conventional techniques. Heart rate was monitored continuously by 3-lead ECG.

ETCO₂ was measured via a neonatal nasal cannula connected to a microstream CO₂ sensor (Cardell monitor, Model 9405). SpO₂ and HR were monitored by pulse oximetry using a reflectance probe (Nelcor Max-Fast) positioned

on the inner aspect of the upper arm. HR was also determined from the ECG allowing measurement when animal activity compromised the integrity of pulse oximetry signals. BP was measured in anesthetized animals using a cuff positioned on the ankle.

- 5 Compound (XXXVI) was dissolved in 20% hydroxypropyl β -cyclodextran (HPBCD) and sterile filtered using a 2 μ syringe filter. Compound (XXXVI), labeled as cmpd (A), was then delivered at a rate of 0.20 mg/kg/min for 5 minutes, followed by reduction of the infusion rate to 0.10 mg/kg/min for 10 minutes. Minute Ventilation and end-tidal CO₂ were monitored. Naloxone HCl (0.05 mg/kg
10 intravenous) was delivered to reverse morphine effects and conclude the experiment. The data showed that cmpd (A) produced a full reversal of end-tidal carbon dioxide increases caused by the opioid, and also increased minute ventilation (Figure 4).

Example 116:

15 Dose-Dependent Effect of Compound (XXXVI) and (L) on Minute Ventilation (MV) in Naive Rats

- All surgical procedures were performed under anesthesia induced by 2% isoflurane in compressed medical grade air. With rats in supine position, the right femoral vein was catheterized using polyethylene tubing (PE-50). This catheter was
20 used for fluid and drug administration. Simultaneously, the right femoral artery was also catheterized for monitoring blood pressure. In order to measure the respiratory parameters in spontaneously breathing rats, trachea was intubated using 13 gauge tracheal tube (2.5mm ID, Instech Solomon, PA).

- After establishing a stable base-line at 1.5% isoflurane, cumulative
25 dose-dependent (0.01, 0.03, 0.1, 0.3, 1, 3, 10 mg/kg) ventilatory responses to compounds (XXXVI) and (L), labeled as cmpd (A) and cmpd (B) respectively, were generated from spontaneously breathing rats. Maximum peak minute ventilatory (MV) values at each dose of corresponding drug were calculated and used for generating ED₅₀ values. The results are shown in Figure 5. Both compounds
30 (XXXVI) and (L) increased minute ventilation in a dose-dependent manner with calculated ED₅₀ values of 0.14 and 0.13 mg/kg respectively.

Example 117:Effect of Compound (CXXI) on Dose-Dependent Minute Ventilation (MV) in Naive Rats

Compound (CXXI), labeled as cmpd (C), was shown to increase
5 minute ventilation in a dose-dependent manner following the procedure above.
Results are shown in Figure 6.

Example 118:Effects of Compound (L) in the Opioid-Treated Rat

10 Following the procedure in Example 6, Compound (L), labeled as
cmpd (B), was shown to reverse the effects of opioid on blood gases and pH in the rat
by increasing pH, SaO₂ and pO₂ and by decreasing pCO₂ levels, as illustrated in
Figures 7A-7D.

15 Example 119:

Effects of Compound (CXLII) in the Opioid-Treated Rat

Following the procedure in Example 6, Compound (CXLII), labeled as
cmpd (D), was shown to reverse the effects of opioid on blood gases and pH in the
rat by increasing pO₂ levels, increasing (SaO₂) oxygen saturation, decreasing pCO₂
20 levels and raising pH, as illustrated in Figures 8A-8D.

Example 120:Effects of Compound (CXLII) on Opioid-Induced Respiratory Depression in the Rat

Following the procedure in Example 5, Compound (CXLII), labeled as
25 cmpd (D), was shown to reverse opioid-induced respiratory depression in the rat by
increasing minute ventilation (MV) as determined by plethysmography. The results
are illustrated in Figure 9.

Example 121:

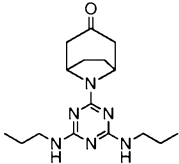
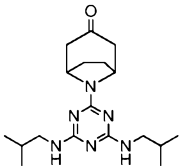
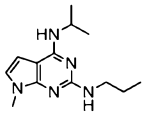
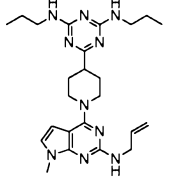
30 Effect of Compounds on Minute Ventilation (MV) and Cardiovascular Parameters in Naive Rats

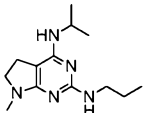
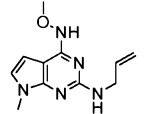
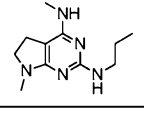
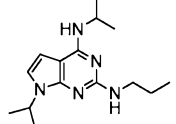
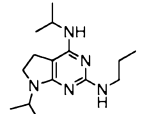
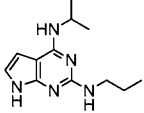
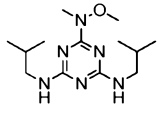
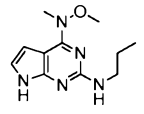
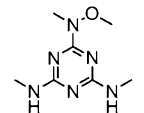
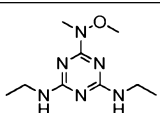
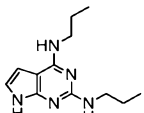
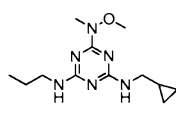
All surgical procedures were performed under anesthesia induced by
2% isoflurane in compressed medical grade air. With rats in supine position, the right
femoral vein was catheterized using polyethylene tubing (PE-50). This catheter was

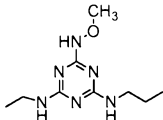
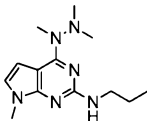
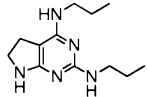
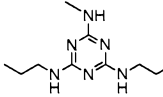
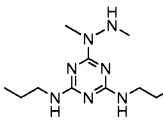
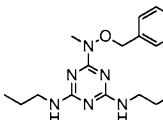
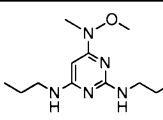
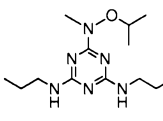
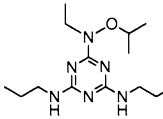
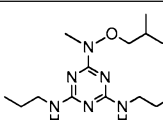
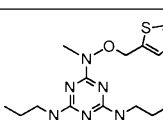
used for fluid and drug administration. Simultaneously, the right femoral artery was also catheterized for monitoring blood pressure and heart rate. In order to measure the respiratory parameters in spontaneously breathing rats, trachea was intubated using 13 gauge tracheal tube (2.5mm ID, Instech Solomon, PA).

- 5 After establishing a stable base-line at 1.5% isoflurane, compounds (typically at a dose of 1 mpk) were administered IV, and ventilatory parameters were generated from spontaneously breathing rats, along with cardiovascular output (mean arterial pressure (MAP) and heart rate). Maximum peak minute ventilatory (MV) responses (MPR), along with changes in minute ventilation versus baseline (ΔMV)
- 10 were obtained as shown in the tables below.

Table 7.

Cmpd	Structure	Formulation	Dose	pH	MV		CV	
					MPR	ΔMV	MAP (mm Hg)	Heart Rate (B/min)
(1,5)-8-(4,6-bis(<i>n</i> -propylamino)-1,3,5-triazin-2-yl)-8-azabicyclo[3.2.1]octan-3-one		20% HPβCD	1mpk	5	213	98	114	308
(1,5)-8-(4,6-bis(isobutylamino)-1,3,5-triazin-2-yl)-8-azabicyclo[3.2.1]octan-3-one		20% HPβCD	1mpk	5	237	137	117	345
N ⁴ -isopropyl-7-methyl-N ² - <i>n</i> -propyl-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine		20% HPβCD	1mpk	5	402	320	118	340
6-(1-(2-(allylamino)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-piperidin-4-yl)-N ² ,N ⁴ -di- <i>n</i> -propyl-1,3,5-triazine-2,4-diamine		20% HPβCD	1mpk	5	154	60	114	350

N ⁴ -isopropyl-7-methyl-N ² - <i>n</i> -propyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine-2,4-diamine		20% HPβCD	1mpk	5	327	224	93	318
CLX, CLXI		20% HPβCD	1mpk	5	182	103	96	336
CXXXI, CXXXII		20% HPβCD	1mpk	4	204	130	101	348
N ⁴ ,7-diisopropyl-N ² - <i>n</i> -propyl-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine		20% HPβCD	1mpk	6	250	155	103	356
CXXXVI, CXXXVII		20% HPβCD	1mpk	4	238	143	98	389
N ⁴ -isopropyl-N ² - <i>n</i> -propyl-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine		20% HPβCD	1mpk	4	259	172	96	387
XXIX		20% HPβCD	1mpk	4-6	253	161	92	371
CXLI, CXLII		20% HPβCD	1mpk	4-6	264	163	93	336
XX		20% HPβCD	1mpk	4-6	213	60	92	432
XXII		20% HPβCD	1mpk	4-6	252	130	95	415
N ² ,N ⁴ -di- <i>i</i> -propyl-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine		20% HPβCD	1mpk	4-6	336	164	94	427
XXV		20% HPβCD	1mpk	4-6	257	126	98	430

N ² -ethyl-6-(methoxyamino)-N ⁴ - <i>n</i> -propyl-1,3,5-triazine-2,4-diamine		20% HPβCD	1mpk	4-6	208	117	95	445
7-methyl-N- <i>n</i> -propyl-4-(1,2,2-trimethylhydrazinyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine		20% HPβCD	1 mpk	4	175	83	93	372
		15/65/20	1 mpk	5	167	89	87	376
N ² ,N ⁴ -di- <i>n</i> -propyl-6,7-dihydro-5H-pyrrolo [2,3-d]pyrimidine-2,4-diamine		20% HPβCD	1 mpk	4	175	93	93	385
		20% HPβCD	1 mpk	6	263	167	99	381
N ² -methyl-N ⁴ ,N ⁶ -di- <i>n</i> -propyl-1,3,5-triazine-2,4,6-triamine		15/65/20	1mpk	5	145	106	92	285
6-(1,2-dimethylhydrazinyl)-N ² ,N ⁴ -di- <i>n</i> -propyl-1,3,5-triazine-2,4-diamine		20% HPβCD	1mpk	5	338	216	97	329
LIII, LIV		20% HPβCD	1mpk	4-6	288	179	96	403
6-(methoxy(methyl)amino)-N ² ,N ⁴ -di- <i>n</i> -propylpyrimidine-2,4-diamine		20% HPβCD	1mpk	4-6	355	243	90	356
6-(isopropoxy(methyl)amino)-N ² ,N ⁴ -di- <i>n</i> -propyl-1,3,5-triazine-2,4-diamine		20% HPβCD	1mpk		271	209	98	378
6-(ethyl(isopropoxy)amino)-N ² ,N ⁴ -di- <i>n</i> -propyl-1,3,5-triazine-2,4-diamine		20% HPβCD	1 mpk	4	308	191	89	351
6-(isobutoxy(methyl)amino)-N ² ,N ⁴ -di- <i>n</i> -propyl-1,3,5-triazine-2,4-diamine		20% HPβCD	1 mpk	4	248	133	87	351
6-(methyl(thiophen-2-ylmethoxy)amino)-N ² ,N ⁴ -di- <i>n</i> -propyl-1,3,5-triazine-2,4-diamine		20% HPβCD	1 mpk	4	213	110	112	411

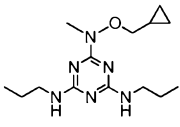
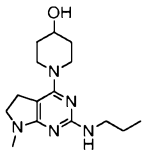
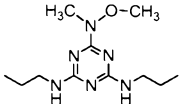
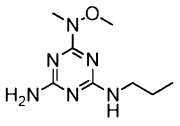
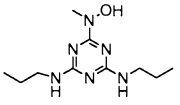
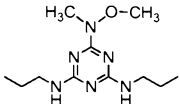
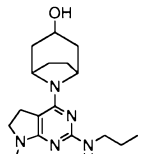
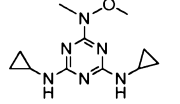
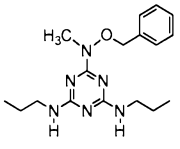
6-((cyclopropyl methoxy)(methyl) amino)-N ² ,N ⁴ -di- <i>n</i> -propyl-1,3,5-triazine-2,4-diamine		20% HPβCD	1 mpk	4	261	152	98	362
CLII, CLIII		20% HPβCD	1 mpk	4	49	0.33	79	245
XXXV, XXXVI		15% DMA 85% D5W	1 mpk	5-6	207	135	87	268
XLVII		20% HPβCD	1 mpk	5	150.73	61.48	109.6	350.52
XLVIII		15/65/20	1 mpk	5	114	30.13	98	300
XXXV, XXXVI		20% HPβCD	1 mpk	4-5	344	210	90	321
CLV, CLVI		20% HPβCD	1 mpk	4	170	57	111	349
XXXIII		20% HPβCD	1 mpk	4-6	147	53	89	480
LIII, LIV		20% HPβCD	1 mpk	4-6	288	179	96	403

Table 8.

Compound	Formulation	Dose	pH	MV		CV			
				MPR	DMV	MAP (mmHg)		HR (B/min)	
						BL	DE	BL	DE
CXX, CXXI	20% HP β CD	1 mpk	4.5	355	243	107	2.3	293	17
CLXX, CLXXI	20% HP β CD	1 mpk	4	175	83	93	-1.0	372	-9.0
CXLIX, CL	20% HP β CD	1 mpk	4	175	93	93	-1.7	385	-28
CLXX, CLXXI	15/65/20	1 mpk	5	167	89	87	1.0	376	-3.8
XXXV, XXXVI	20% HP β CD	1 mpk	5	267	164	101	-1.7	335	43
CXLIX, CL	20% HP β CD	1 mpk	6	263	167	99	-3	381	-18
XXXI	20% HP β CD	1 mpk	4	140	43	101	2.6	372	2.5
CXIII, CXIV	20% HP β CD	1 mpk	4	167.1	46	101	-4	368	23
CXV, CXVI	15/65/20	1 mpk	4	155.7	33.8	97	-5	374	-5
CXVII, CXVIII	20% HP β CD	1 mpk	4.5	143.8	15	92	-8	365	-2
LXXII, LXXIII	20% HP β CD	1 mpk	4	176	82	358	8	108	-4
LXXVI, LXXVII	20% HP β CD	1 mpk	4	308	191	351	15	89	-2
LXXXII, LXXXIII	20% HP β CD	1 mpk	4	248	133	351	19	87	10
LXXXIV, LXXXV	20% HP β CD	1 mpk	4	213	110	411	15	112	-1
XCI, XCII	20% HP β CD	1 mpk	4	261	152	362	63	98	-2

Example 122:Effect of Compound (XXXVI) on Benzodiazepine-Induced Respiratory Depression5 (BIRD)

In one aspect, the objective of the current study was to evaluate the effects of an intravenous infusion of compound (XXXVI) on respiratory depression, induced by midazolam in rats.

Procedures:

Compound (XXXVI) was dissolved in 20% hydroxypropyl-beta-cyclodextran in sterile water, and titrated to a pH of 4-8 using pH paper and NaOH or HCl, resulting in a clear, stable solution at a concentration of 1.5 mg/mL. Other
5 compounds: morphine sulfate, supplied as 10 mg/mL solution by (Baxter, Inc) and midazolam, supplied as 5 mg/mL solution (Hospira, Inc.)

Materials:

Male Sprague-Dawley rats (Harlan, Inc.), 250-350 g at time of dosing, surgically prepared by Harlan with jugular vein cannulas. 12 Chamber
10 Plethysmography System with temperature/humidity compensation (Epstein et al., 1980, J. Apply Physiol. 49:1107-1115); From Buxco, Inc. (PLY 3223; Buxco, Inc, Wilmington, NC, USA) Biosystem XA, software, v2.11.1. Customized 12 site automated infusion system (Harvard Apparatus; Instech, Inc)

Methods:

15 Rat whole body plethysmography was used to evaluate and quantify minute ventilation and the pattern of breathing. A respiratory waveform was generated from the exchange of air between the animal and the chamber. This exchange induced changes in air volume that were measured with a pressure transducer, constituting the respiratory waveform. Atmospheric temperature and
20 humidity were also measured using temperature and humidity probes which sampled chamber conditions. A compensation factor was then determined and applied to the respiratory waveform using a standardized algorithm (Epstein et al., 1980, J. Apply Physiol. 49:1107-1115) to compensate for respiratory conditioning, which was reported as the parameter COMP (see appendix).

25 All animals were acclimated to plethysmography chambers for at least 1 hour, or until animals were no longer restless (up to 2 hours) prior to data collection. Bolus intravenous (IV) dosing was administered at a rate of 5-10 seconds per dose, and catheters were flushed with 350 µL of sterile saline to be sure of complete drug delivery. All 12 animals (6 vehicle; 6 drug treated) were dosed simultaneously within
30 one 60 second period. For intravenous infusions, vehicle or test compound was prepared at a 0.1 mg/mL stock as described, and administered with Harvard apparatus infusion pumps. Compound (XXXVI) was given via infusion over a 30 minute period at a rate of 20 µL/min/0.3 kg, to give a dose of 0.1 mg/kg/min, beginning 5 minutes after the bolus IV administration of midazolam. None of the included studies were

performed blinded, due to the logistics of simultaneously dosing multiple animals. All plethysmography data was recorded automatically by the Buxco equipment.

Statistical Analysis:

Respiratory data were collected on a breath-by-breath basis and averaged into 1 min time bins for data analysis. For each designated acquisition phase, which is the time between doses, percent change from pre-treatment baseline values were calculated for each cohort on multiple ventilatory parameters including respiratory frequency (f), tidal volume (TV), accumulated volume (AV), minute ventilation (MV), inspiratory time (Ti), expiratory time (Te), peak inspiratory flow (PIF), peak expiratory flow (PEF), relaxation time (RT), end inspiratory pause (EIP), end expiratory pause (EEP), delta volume (DV), expiratory flow at 50% TV (EF50), rejection index (Rinx), compensation (Comp), enhanced pause (Penh), pause (PAU), PEF rate (Rpef), relative humidity (RH), and atmospheric temperature (Temp).

Each parameter was compared to vehicle in order to calculate percent difference, using area under the curve (AUC) and peak response values for each defined acquisition period using a customized visual basic restructure analysis macro. Additionally, percent reversal of drug induced respiratory depression by compound was calculated using the mean respiratory depression derived from all vehicle (or untreated) animals, compared to the mean pre-treatment baselines of all animals in the study.

Results:

Compound (XXXVI) (0.1 mg/kg/min) reversed the BIRD induced decrease in MV by 100 by the end of the infusion period (t = 38). Compound (XXXVI) had an effect to reverse the effects of midazolam on MV (Figure 15), TV (Figure 16), AV, Te, PIF, PEF, and EEP, and had no obvious effect on f (Figure 17), Ti, RT, EIP, dv, EF50, Rinx, Comp, Penh, PAU, Rpef, RH, and Temp. Small increases in minute ventilation in all groups were often seen during IV bolus injections which were treated as injection artifacts due to animal arousal, and had no other apparent impact on ventilation.

Potential adverse events were monitored, and there were no adverse behavioral effects observed following administration of compound (XXXVI) at the doses tested. The results of these experiments demonstrated that compound (XXXVI) reverses midazolam induced-respiratory depression and appears to be well tolerated in rats at the doses tested.

Example 123:Effect of Compound (XXXVI) on Hypercapnia

In one aspect, the objective of the study was to evaluate the effects of
5 Compound (XXXVI), administered by intravenous infusion, on the hypercapnic
ventilatory response (HCVR) in rats.

Vehicle, 20% hydroxypropyl-beta-cyclodextran in sterile water, was
added to pre-weighed compound and mixed thoroughly, resulting in a clear solution.
A 1.5 mg/mL stock was created to give an infusion dose of 0.10 mg/kg/min. A
10 separate 0.45 mg/mL stock was created to give an infusion dose of 0.03 mg/kg/min.
All compound solutions and vehicles were titrated to have a pH between 4-8, using a
pH paper and titrating with NaOH or HCl solution.

Male Sprague-Dawley rats (Harlan, Inc.), 250-350 g at time of dosing,
had been surgically prepared by Harlan to contain jugular vein cannulas. A 12
15 chamber plethysmography system with temperature/humidity compensation (Epstein
et al., 1980, J. Apply Physiol. 49:1107-1115) from Buxco, Inc. (PLY 3223; Buxco,
Inc, Wilmington, NC, USA) using Biosystem XA software, v2.11.1 and a customized
12 site automated infusion system (Harvard Apparatus, Instech, Inc). Gas mixer
(CWE Inc.) was used for this experiment to give concentrations of hypercapnia (3%
20 CO₂, 21% O₂, balance nitrogen). Three tanks containing 100% O₂, CO₂, and nitrogen
were attached to the gas mixer, with the customized gas mixture fed to each
plethysmograph at a rate of 2 L/min.

Rat whole body plethysmography was used to evaluate and quantify
minute ventilation and the pattern of breathing. A respiratory waveform was
25 generated from the exchange of air between the animal and the chamber. This
exchange induced changes in air volume that were measured with a pressure
transducer, constituting the respiratory waveform (Lomask M., 2005, "Respiration
measurement in the whole body plethysmography," Buxco Inc., retrieved from
[http://www dot buxco dot com/ downloads/ LomaskWBP dot pdf](http://www.dotbuxco.com/downloads/LomaskWBP.pdf)). Atmospheric
30 temperature and humidity were also measured using temperature and humidity probes
that sampled chamber conditions. A compensation factor was then determined and
applied to the respiratory waveform using a standardized algorithm (Epstein et al.,
1980, J. Apply Physiol. 49:1107-1115) to compensate for respiratory conditioning,
which was reported as the parameter COMP.

All animals were acclimated to plethysmography chambers for at least 1 hour, or until animals were no longer restless (up to 2 hours prior to data collection). Minute ventilation (MV) was calculated by the Biosystem XA software from direct measurements of tidal volume (TV) and respiratory frequency (f) using the formula

5 $MV = TV \times f$. Minute ventilation (mL/min) is a common endpoint for evaluating ventilatory performance. The protocol included compound (XXXVI) given as a 20 minute infusion, followed by a 20 minute exposure to 3% hypercapnia in addition to the compound (XXXVI) infusion. After 20 minutes of hypercapnia, the compound (XXXVI) infusion continued for an additional 10 minutes, resulting in a total

10 compound (XXXVI) infusion time of 50 minutes. Each experiment included 6 animals receiving compound (XXXVI) (0.03 or 0.10 mg/kg/min) tested against 6 animals receiving vehicle, all of which were challenged with hypercapnia (3%). Animals were continuously monitored and observed for adverse behavioral effects. Such findings were recorded into laboratory notebooks for each individual animal

15 tested.

Statistical Analysis

Respiratory data was collected on a breath-by-breath basis and averaged into 1 min time bins for data analysis. For each designated acquisition phase, which is the time between doses, AUC percent change from pre-treatment

20 baseline values were calculated for each cohort on multiple ventilatory parameters including, respiratory frequency (f), tidal volume (TV), accumulated volume (AV), minute ventilation (MV), inspiratory time (Ti), expiratory time (Te), peak inspiratory flow (PIF), peak expiratory flow (PEF), relaxation time (RT), end inspiratory pause (EIP), end expiratory pause (EEP), delta volume (dV), expiratory flow at 50% TV

25 (EF50), rejection index (Rinx), compensation (Comp), enhanced pause (Penh), pause (PAU), PEF rate (Rpef), relative humidity (RH), and atmospheric temperature (Temp). Each parameter was compared to vehicle in order to calculate percent difference, using area under the curve (AUC) and peak response values for each defined acquisition period using a customized visual basic restructure analysis macro

30 (Lopotosky, S. Galleon Buxco Restructure tool, v5.2, 2008). All of the data analysis for the single, stand-alone studies was done using the restructure analysis macro (Lopotosky, S. Galleon Buxco Restructure tool, v5.2, 2008). All merged data analysis with both doses was performed in Graphpad Prism for MV, TV, and f only, for hypercapnia studies. Additionally, percent increase was calculated based on the

cohort average immediately prior to the hypercapnic challenge to the group's peak response. For merged hypercapnia studies, t=62 to t=67 was used.

Results and Discussion:

Administration of compound (XXXVI) stimulated respiration in naive
5 animals at 0.10 mg/kg/min, with little or no effect at 0.03 mg/kg/min. Furthermore,
when animals received compound (XXXVI), exposure to hypercapnia (3% CO₂)
resulted in an increased MV response in a dose dependent manner when compared to
vehicle treatment alone. Compound (XXXVI), at 0.03 or 0.1 mg/kg/min IV, resulted
10 in the augmentation of the hypercapnia ventilatory response (HCVR), at the higher
dose of 0.10 mg/kg/min, with no effect at 0.03 mg/kg/min. The 0.03 mg/kg/min and
vehicle groups resulted in a 60% facilitation of the HCVR, from t=62 to t=67. The
0.10 mg/kg/min demonstrated an increase of 44% in MV during the HCVR challenge
at the same time points, in addition to an elevated MV due to compound (XXXVI)
alone. Compound (XXXVI) at 0.03 mg/kg/min against HCVR resulted in an effect
15 on PIF only, with no discernable change in f, TV, AV, MV, Ti, Te, PEF, RT, EIP,
EEP, dv, EF50, Rinx, Comp, penh, PAU Rpef, RH, or Temp. The 0.10 mg/kg/min
dose showed an effect on f, TV, AV, MV, Ti, Te, PIF, PEF, EIP, EF50, Comp, and
RH, with no discernable change in EEP, dV, Rinx, Penh, PAU, Rpef, and Temp.
These data suggest that compound (XXXVI), given as an infusion, may enhance the
20 ventilatory effects of hypercapnia, resulting in facilitation of ventilation during acute
hypoxemia. In addition, there were no adverse clinical observations associated with
compound (XXXVI) at the doses tested.

Example 124:

25 Effect of Compound (XLII) on Respiratory Rate, Tidal Volume, Minute Volume and
5-min Average Change in Minute Volume in Rat

General Methods:

Adult male Sprague Dawley rats (250-350 g body weight; Harlan,
Indianapolis, IN, USA) were anesthetized with isoflurane in oxygen. The femoral
30 vein was cannulated to administer compounds. Body temperature was maintained
between 36.0 and 37.2 °C throughout the experiment. The cervical portion of the
trachea was cannulated and attached to a rat-sized pneumotachometer for measuring
tracheal airflow. After surgical instrumentation was complete, isoflurane was slowly
discontinued, while urethane (1.8 g/kg) was administered intravenously over 10-15

minutes to maintain anesthesia. Rats were permitted to breathe spontaneously and inspire 100% oxygen. At least 30-45 minutes after discontinuing isoflurane, baseline tracheal airflow was recorded for 20-30 minutes prior to compound administration. Vehicle and test compound were administered intravenously over 15-25 seconds and at a constant volume (1 mL/kg). At least 15-min elapsed between each dose of compound administered. Tracheal airflow was recorded continuously before, during and after compound administration. Tidal volume was derived from the integral of airflow, and respiratory rate was derived from the number of inspiratory cycles per minute. Minute volume was calculated as the product of tidal volume and respiratory rate (Figure 32).

Results:

Compared to vehicle, Compound (XLII) increased both respiratory rate and tidal volume, and their product minute volume.

15 Example 125:

Effect of Compound (CLXXII) on Respiratory Rate, Tidal Volume, Minute Volume and 5 min Average Change in Minute Volume in Rat

General Methods: See Example 124 above

Results

20 Compared to vehicle, Compound (CLXXII) increased both respiratory rate and tidal volume, and their product minute volume.

Example 126:

Effect of Compound (XXXV) on BK Potassium Channel Current in GH3 Cells

25 *Experimental Procedures*

Stock solutions of the test article were prepared in dimethylsulfoxide (DMSO) and stored frozen. Test article concentrations were prepared fresh daily by diluting stock solutions into a physiological saline solution (composition in mM): KCl, 125; CaCl₂, 8.5; HEPES, 10; EGTA, 11.25; pH adjusted to 7.2 with KOH (prepared weekly and refrigerated until used). All test solutions contained 0.1% DMSO.

GH3 cells were grown in culture using standard procedures. Ionic currents were measured from inside-out patches of GH3 cells. Channel activity was monitored in symmetrical K⁺ conditions with a holding potential of -60 mV.

Activities before and in the presence of each concentration of test articles were recorded for ≥ 3 minutes, respectively.

Data Analysis

- 5 Data acquisition and analyses were performed using the suite of pCLAMP (Ver. 8.2) programs (MDS-AT, Sunnyvale, CA. Percent inhibition by test article was calculated using the equation: $100 \cdot (\text{NPo}_{\text{control}} - \text{NPo}_{\text{test}}) / \text{NPo}_{\text{control}}$

Results

- Compound (XXXV) was evaluated at 1 and 10 μM , and almitrine, a positive control, was evaluated at 1 μM . Channel effects were estimated from the change in activities at steady-state after application of test articles. The effect of Compound (XXXV) is summarized in Table 9. A sample recording before and after 1 μM (XXXV) and all points histogram is showed in the Figure 21.

15 Table 9.

Effect of Compound (XXXV) on the single BK potassium channel expressed in GH3 cells recorded in inside-out patches

Cell ID	Channel Amplitude (pA)	NPo			Inhibition (%)		
		control	(XXXV) (mM)		Almirite (mM)	(XXXV) (mM)	
			1	10		1	10
C 05 SP 101008 0000	-14.3	0.013	0.0076	0.0057	0.0011	41.5	56.2
E 05 SP 101008 0000	-17.8	0.042	0.037	0.023	0.00090	11.9	45.2
A 05 SP 101012 0000	-15.5	0.037	0.032			13.5	
B 05 SP 101012 0000	-16.6	0.066		0.051			22.7
Average	-16.0	0.040	0.014	0.020	0.0010	22.3	41.4
SD	1.4	0.022	0.016	0.027	0.0001	16.7	4.5

NPo: total channel open probability.

- 20 $\text{Inhibition (\%)} = 100 \cdot (\text{NPo}_{\text{control}} - \text{NPo}_{\text{test}}) / \text{NPo}_{\text{control}}$
Washout was performed to the patch C 05 SP 101007 0000 before and after application of 1 μM almitrine, to the patch B 05 SP 101012 000 after application of 10 μM (XXXV).

Summary and Conclusions

As illustrated in Figure 34, Compound (XXXV) exerted concentration-dependent inhibition of the native BK channel expressed in GH3 cells. At the highest concentration tested (10 μ M) Compound (XXXV) reduced total
5 channel open probability by 42%.

Example 127:Effect of Compounds on Thallium Flux Through Rat TASK-1 (KCNK1) and Human TASK-3 (KCNK9) Channels10 *Experimental procedure**(a) Seed cell plates:*

CHO cells expressing recombinant tetracycline-inducible rat KCNK3/TASK-1 (KCNK3-CHO cells) were plated in poly-D-lysine coated 384-well plates at a density of 6,000 cells/well (50 μ l/well of 120,000 cells/mL) and allowed to
15 incubate for 72 hrs in the presence of 5% CO₂ and 1 μ g/mL tetracycline at 30°C. HEK cells expressing recombinant tetracycline-inducible human KCNK9/TASK-3 (KCNK9-HEK cells) were plated at a density of 15,000 cells per well (50 μ l/well, 300,000 cells/mL) and incubated overnight at 37°C and 5% CO₂ in the presence of 1 μ g/mL tetracycline.

20 *(b) Preparation of compound containing plates:*

Drug plates were generated from 10 mM 100% DMSO mother plates. Compounds were transferred to 384-well drug plates and titrated with sequential 1:3 dilutions in 100% DMSO for a total of 9 dilutions. A dilution plate is made by taking 2.4 μ l from the mother plate and adding to 17.6 μ l of assay buffer for a 12% DMSO
25 dilution plate. From this dilution plate, a final daughter plate is generated by taking 1 μ l of the dilution plate and adding to 40 μ l of assay buffer for a final DMSO concentration of 0.3%. Each compound was evaluated in duplicate and the concentration range evaluated was 3 nM to 30 μ M.

Assay protocol:

30 When thallium was added to extracellular solution with a stimulus to open channels, Tl⁺ flowed down its concentration gradient into the cells and channel activity was detected with an indicator dye, FluxOR™, that increased in cytosolic fluorescence. The FluxOR™ indicator dye was loaded into cells as a membrane

permeable acetoxymethyl ester. On the day of each assay, FluxOR™ assay buffer was made fresh from Hank's Balanced Saline Solution (HBSS) buffered with 20 mM HEPES and pH adjusted to 7.4 with NaOH. Dye loading solution was prepared per manufacturer's instructions, and 25 µl of dye solution applied to each well with a multidropper after plating medium was removed manually from cells. Dye was allowed to load for 90 minutes at room temperature in the dark.

After the 90min dye loading incubation and subsequent manual dye removal, 24 µl of the drug daughter plate was transfer to cell plates by a cybi-well system and then incubated at room temperature for 20 minutes to allow for equilibration within wells. Stimulation buffer was prepared from 5X chloride-free buffer, thallium, and potassium sulfate containing 5 times the desired final assay concentration of 10 mM K⁺ 2.8 mM TI⁺. Cell plates were then transferred to an FDSS 6000 kinetic imaging plate reader (Hamamatsu). Fluorescence at 525 nm (excitation 488 nm) was measured for 10 seconds at 1Hz to establish baseline for the entire plate. After baseline was established, 6 µl/well of stimulation buffer was added and fluorescence signal recorded for another 140 seconds.

Data analysis

From the fluorescence signals in the absence and presence of Galleon compounds, Inhibitory concentration curves were plotted and IC₅₀ values were estimated using a curve fitting algorithm.

Results

The results are summarized in Table 10. Using TI⁺ flux as an indicator of rat TASK-1 and human TASK-3 activity, some compounds displayed blockade of rTASK-1.

Table 10.

IC₅₀ values for inhibition of rat TASK-1 and hTASK-3

Compound	hTASK-3	rTASK-1
	IC₅₀ (µM)	IC₅₀ (µM)
Cmpd (XXXVI)	>30	25
Cmpd (XLII)	>30	0.05
Cmpd (XLVI)	>30	0.60
Cmpd (CLXXII)	>30	0.01
Cmpd (CXXI)	>30	0.22
Cmpd (CLXX)	>30	0.16

Example 128:Effect of Compound (XXXVI) on Ventilation in Human Volunteers

N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) was administered to humans during two
5 single dose studies of similar design.

The first study (GAL-021-101) was a single, ascending dose study in healthy subjects. Mild/moderate burning sensation at the infusion site was the only adverse event that differed from placebo from drug-treated subjects. At the highest dose (0.96 mg/kg/h) stimulation of minute ventilation and reduction of end tidal CO₂
10 (ETCO₂) were noted.

The second study (GAL-021-102) extended the dose range explored during the initial study by a factor of 2 and established the maximum respiratory stimulatory dose in the healthy subjects without concomitant use of opioids or anesthetic agents. At the 0.96 mg/kg/h, similar changes in minute ventilation was
15 noted with greater effects at the highest dose (1.92 mg/kg/h).

*Phase I Data**(a) Summary of Phase I Clinical Safety*

The first study (GAL-021-101) was a randomized, double-blind, placebo controlled, nine-period, ascending single dose study in three alternating
20 cohorts of healthy subjects. Three cohorts of 10 subjects each were randomized to treatment in a ratio of 4:1 (8 treated, 2 placebo) in a rotating panel design (Figure 35). Subjects in the first cohort participated in dosing periods 1, 4, and 7, with the second cohort participating in dosing periods 2, 5, and 8, and third cohort participating in dosing period 3, 6, and 9. The subjects who received placebo in the first dosing
25 period also received placebo in the second and third dosing periods. Similarly, drug-treated subjects received drug in all three dosing periods. After an overnight fast, subjects received an intravenous infusion of N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) or placebo then PD, PK, and safety evaluations were conducted during the next 24 hours.

30 Eight intravenous dose levels were administered with the first seven doses being fixed rate infusions (0.1-0.96 mg/kg/h) for 1, 2, 3, or 4 hours and the last used a loading dose (0.72 mg/kg/h for 1 hour) followed by a maintenance dose (0.36 mg/kg/h for 3 hours).

The second study (GAL-021-102) was a randomized, double-blind, placebo-controlled, four-period, single-rising dose study in alternating cohorts of healthy subjects. Two cohorts of nine subjects each were randomized to treatment in a ratio of 2:1 (6 treated, 3 placebo) in a rotating panel design. Subjects in the first cohort participated in dosing periods 1 and 3, with the second cohort participating in dosing periods 2 and 4. The subjects received placebo at most once during the study. After an overnight fast, subjects received an intravenous infusion of N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) or placebo then PD, PK, and safety evaluations were conducted during the next 24 hours.

Three intravenous dose levels were administered with fixed rate infusions (0.96-1.92 mg/kg/h) for 2 hours. During the 3rd treatment period, two subjects had increasing ventilatory efforts and declining ETCO₂ (nadirs: 22 and 29 mmHg), and the infusions were stopped with rapid diminution of the respiratory efforts. The stopping criteria for further dose escalation had been met. During the 4th and final treatment period, subjects were reassigned to the two lower dose levels based on their previous treatment to increase the total number of subjects receiving these dose levels.

A third study, a two-part, four-treatment period, double blinded, placebo controlled, crossover, stepped infusion study, evaluated ventilatory PD effects of N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) on respiratory drive in a model of opioid induced respiratory depression. In Part 1, dynamic end-tidal CO₂ forcing technique was used. This is a progressive hypercapnia resulting in targeted minute ventilation to 20 L/min. Once achieved maintain (clamp) the PCO₂ at the same level throughout the remainder of the treatment period to remove the confounding influence of CO₂ changes on minute ventilation.

In each part, subjects were randomized to two treatments (placebo or N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI)) with each subject receiving each treatment once. In Part 2, the treatment sequence and opioid doses from Part 1 were repeated under ambient air conditions and addition of pain assessments. All treatment periods were subdivided into 7 segments (treatment period details provided in Figure 36) with a sequential

design. Two dose levels of alfentanil and two dose levels of (XXXVI) were included in each treatment period to provide a preliminary assessment of the dose response.

In Part 2, pain was assessed to determine if N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) impaired the opioid pain reduction using transcutaneous electrical stimulation over the tibia.

Twenty three subjects participated in the study. Twelve subjects completed both treatment periods of Part 1 and 8 subjects participated and completed both treatment periods of Part 2. Three subjects completed one treatment period of Part 1. Of these subjects, 2 discontinued the study after completing the first treatment period and a 3rd subject discontinued before completing segment 2 in the second treatment period. Of these 3 subjects, one successfully completed Part 2. Six subjects dropped out the study between just before starting the first segment to completion of segment 2. If segment 2 was completed subjects completed the remaining 5 segments of the treatment period. The primary reason for drop outs by these subjects was procedure-related (e.g., arterial line placement, mask associated anxiety) or difficulty accommodating to the hyperventilation induced by the inspired supplemental CO₂ induced hypercapnia.

As illustrated in Figure 36, during each study part, subjects were randomly assigned to either N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) or placebo during the first treatment period and received the other during the second treatment period. All subjects were pretreated with ondansetron and metoclopramide due severe nausea and vomiting in pilot study secondary to alfentanil administration. During Part 1 segment 1, baseline ventilatory parameter were assessed after freely breathing ambient air for ~20 minutes during a 10 minute assessment period at the end of each segment denoted by blue inverted triangles (▼). During segment 2, CO₂ concentrations were increased slowly using gas mixer until the subject achieved a minute ventilation of 20 L/min. Alfentanil was titrated in segment 3 to achieve 25-35% reduction in end tidal minute ventilation and inhaled CO₂ adjusted to maintain the same end-tidal PCO₂ as at the end of segment 2. Similar CO₂ adjustments were made throughout the remaining segments. In segment 4, low dose N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) was administered initially by rapid infusion (2.0 mg/kg/min) and then maintenance infusion (0.4 mg/kg/h) to

approximately a low dose, steady state concentration. In segment 5, a second rapid infusion (2.0 mg/kg/h) and greater maintenance infusion (1.1 mg/kg/h) were used to assess the primary endpoint (minute ventilation) at high steady state concentration. Thereafter (segment 6), the individualized loading and maintenance dose of alfentanil (from segment 3) were doubled and ventilatory parameters assessed. At the beginning of the final segment 7, the alfentanil and N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI)/placebo infusions were stopped and subjects observed. After establishing the individual alfentanil dose in Part 1, segment 1, the same infusion rates were used for all remaining segment in Parts 1 and 2. For Part 2, the same segment progression was used while breathing ambient air without use of CO₂ clamping techniques. In Part 2, transcutaneous electrical stimulation (TENS) over the tibia was used to establish pain threshold for detection and maximum tolerability. During the pain testing, current progressive increase with subjects pushing a button to note onset of pain and maximum tolerable pain, at point the current stopped. The pain assessments are performed during segments 1-6 before the ventilatory assessment interval.

(b) Summary of Phase I Pharmacodynamics

Pharmacodynamic (PD) evaluations included tidal volume, respiratory rate, minute ventilation, end-tidal CO₂, and transcutaneous hemoglobin oxygen saturation (SpO₂). Baseline respiratory data was acquired for 1 hour before dosing and the parameters average over that period after removal of recorded regions contain artifacts by treatment-blinded polysomnographic experts before analysis. PD data was collected for ~1 hour after completing the infusion. The time weighted percent change from baseline was calculated for all respiratory parameters. The first 2 hours of data from groups 6 and 7 (0.72 mg/kg/h for 2 hour or more) was pooled for PD analysis. At all doses, change in respiratory rate was small and usually < 10%. Tidal volume changes were also small with only the 0.96 mg/kg/h dose having a consistent increase < 10% (Figure 37).

To further evaluate the respiratory changes, the responses were integrated over the first 2 hours after the start of the infusion. Minute ventilation did not change significantly except at the two highest infusion rates with 7-16% increases noted (Figure 38A) using the Dräger pneumotachometer-based system. End-tidal CO₂ decreased in parallel to minute ventilation increases with an integrated reduction of ~6% (Figure 38B). The onset of effects on minute ventilation and ET-CO₂ were

rapid with > half maximal effect observed by the 7.5 minutes (first assessment point). A similar pattern of changes in minute ventilation, tidal volume and respiratory rate (Figures 38C-D) were observed with NOX-T3 inductance plethysmography-based system with ~24% increase in minute ventilation. Transcutaneous hemoglobin O₂ tension was not significant different from placebo except at the 0.96 mg/kg/h dose with an average change of +0.85% vs. -0.05% ($p < 0.05$).

The second study was conducted at the same clinical site as the first study and similar PD assessments and equipment were utilized. The first dose had an identical infusion rate to the first study (0.96 mg/kg/h) with an extended duration of 2 hours. Minute ventilation increased rapidly with mean increase of 15.4% during the 2-hour infusion period, which yielded similar results to the first study (16.1%). The middle dose had a similar increase (13.6%), while the high dose had a greater increase (24.3%). The minute ventilation changes were statistically significant at all 3 dose levels (Figure 39A). The effects on tidal volume and respiratory rate underlying the changes in minute ventilation were more variable with the low dose having a primary effect on tidal volume, the middle dose on respiratory rate, and the high dose on the combination of both. End tidal-CO₂ was also reduced at all dose levels with highest dose having mean reduction >8% over the infusion period (Figure 39B). Changes at the low and high dose were statistically different from placebo for ETCO₂ and tidal volume. Half-maximal effects occurred before or just after the 5 minute assessment (first timepoint measured) in minute ventilation, tidal volume, and ETCO₂ (Figures 39B-D). A rapid initial response was previously observed at lower infusion rates in the first study, but tended to decline soon thereafter, while the PD responses were sustained at dose ≥ 0.72 mg/kg/h.

Similar to the highest infusion rate in the first study (0.96 mg/kg/h), hemoglobin O₂ saturation (SpO₂) increased rapidly after initiation of the infusion with statistically significant differences noted from 25 to 75 minutes for the low and high doses (Figure 40). The integrated effects over the two-hour infusion increased 0.60% and 0.76% for low and high doses, respectively, vs. placebo (0.13%, $p < 0.05$). For the middle dose, the 1-2 hour period had a greater increase in minute ventilation (17.2%) than the first hour (10.0%) and also had a statistically significant increase in SpO₂ vs. placebo (0.41% vs. -0.02%, $p < 0.05$).

During the respiratory depression Proof-of-Concept study (GAL-021-104), ventilatory parameters were captured continuously, which were integrated over

the final ten-minute interval as the primary endpoints with segment 5 being the primary inferential statistical comparison. The initial CO₂ escalation (Segment 2) was performed slowly to increase minute ventilation to 20 liters/min (~2.5-fold baseline) (Figure 41A). Alfentanil was titrated thereafter with ~²/₃ reduction in CO₂ stimulated increment in minute ventilation (37% absolute reduction). With the additional of a minimally stimulatory (XXXVI) dose (0.4 mg/kg/h), there was trend in minute ventilation toward separation from placebo (p<0.07), which reached statistical significance at the higher infusion rate (1.1 mg/kg/h) (p<0.0001). With the doubling of alfentanil loading dose and infusion rate in the sixth segment, minute ventilation declined for both GAL-021 and placebo while statistically significant separations continued between the 2 treatments (p < 0.005). For tidal volume (Figure 41B) and respiratory rate (Figure 41C), similar patterns of the statistically significant difference were noted.

During Part 2 of the study, subjects received the identical alfentanil loading doses and infusion rates as in Part 1. Subjects were allowed to breathe ambient air and no attempt was made to regulate end-tidal CO₂ or minute ventilation. Pain was also assessed using a transcutaneous electrical nerve stimulation device (TENS) placed over the anterior tibia area, so that minimal muscular effects were produced. During testing, current progressively increased producing a current threshold associated with the onset of pain and maximum tolerable pain (Figure 36). With the administration of alfentanil, the pain onset threshold increased (Figure 42). N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) administration did not diminish the pain onset or maximum tolerable thresholds.

With the initiation of the alfentanil infusion, minute ventilation decreased (Figure 43A). Placebo treated subjects remained stable until the higher dose alfentanil in segment 6 when it further declined. Similar to the Part 1, minute ventilation separated from placebo treatment with low dose N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) treatment and reached statistical significance with high dose in segment 5. While the high dose of alfentanil diminished N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) stimulation in Part 1 (segment 6), there was no diminution in minute ventilation under room air conditions. Consistent with known opioid effects, end tidal CO₂ increase and further increased

with the high dose alfentanil dose (Figure 43B). N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) administration tended to reduce end tidal CO₂ concentrations with statistically significance noted with high dose alfentanil (segment 6). Respiratory rates were not different (Figure 43C). Tidal volume increased with high dose N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) compared to placebo treatment with both the low and high dose alfentanil infusions (Figure 43D).

During Part 1 and Part 2, N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) had consistent effects compared to placebo that were clinically and statistically significant at the higher infusion rate (1.1 mg/kg/h). The effect was independent of the presence of exogenous CO₂ or endogenous retention of CO₂ secondary to opioid administration. The low, minimally stimulatory dose of N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) separated from placebo treatment with minute ventilation changes approached statistical significant without achieving it. Similar low dose N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) trends were noted in both study parts. The increase in minute ventilation tended to be driven by increase in tidal volume noted in both study parts. Changes in respiratory were noted only in Part 1. Overall, N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) improved ventilatory status after opioid administration consistent with previous observation in rats and non-human primates. The improved ventilatory status after N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) administration did not compromise the analgesic effects of alfentanil and suggesting that current difficulty balancing of opioid analgesia and respiratory depressive effects may be less nettlesome when the 2 pharmacologic agents are coadministered.

(c) Summary of Phase I Pharmacokinetics

In general, the overall shape of the plasma concentration-time profile was similar in both studies. Plasma concentrations rose rapidly during the infusion and fell sharply initially and then gradually after the infusion. The mean maximum plasma concentrations (C_{max}) were reached generally at the end of infusion or the end

of loading dose infusion in the case of the biphasic infusion, as illustrated in Figure 44.

In the first study after the end of infusion, all plasma concentration-time profiles displayed apparent bi-exponential decay with a steep distributional phase and a gradual terminal phase with a mean terminal half-life ($t_{1/2}$) ranging from 4.3 to 6.5 h (Figure 44A). The pharmacokinetics of N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) in healthy volunteers was best described by a two-compartmental model in general with a distributional half-life of less than 20 min. The mean systemic plasma clearance values (CL_p), were approximately half the hepatic blood flow rate in humans. The mean steady-state volume of distribution values (V_{ss}), ranging from 1.7 to 2.5 L/kg, were roughly 2-3 times the total body water in humans, suggesting that N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) was highly distributed to tissues. The plasma concentration at one-hour into infusion, C_{1h} (range: 54.9-930 ng/mL), was dose-proportional at all tested infusion rates. Similarly, total systemic exposure ($AUC_{0-\infty}$) was also dose proportional. The C_{1h} and AUC meet the statistical requirement for dose proportionality. The intra-subject variability is generally less than inter-subject variability for $t_{1/2}$, CL_p , and V_{ss} .

Table 11A. Mean Pharmacokinetic Parameters for N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-l-hydroxylamine Hydrogen Sulfate (XXXVI) in Human Plasma

Infusion Rate (mg/kg/h)	Duration (h)	N	Dose (mg/kg)	T _{max} (h)	C _{max} (ng/mL)	C _{1H} (ng/mL)	AUC ₀₋₂₄ (ng•h/mL)	AUC _{0-∞} (ng•h/mL)	AUC _{0-∞} /D (ng•h/mL)	t _{1/2} (h)	CL _p (mL/min/kg)	V _z (L/kg)	V _{ss} (L/kg)
0.1	1	8	0.102	0.86 (0.75-0.97)	71.4 (17)		160 (16) ^b	144 (27)	1416 (27)	4.29 (43)	11.8 (39)	4.37 (36)	1.72 (33)
0.3	1	16	0.300	0.97 (0.75-0.97)	203 (22)		388 (14)	397 (14)	1324 (14)	5.87 (22)	12.6 (15)	6.40 (19)	2.34 (24)
0.6	1	7	0.600	0.97 (0.97-0.97)	449 (15)		901 (7.2)	923 (7.3)	1539 (7.5)	6.01 (11)	10.9 (7)	5.63 (9.4)	2.20 (14)
0.96	1	6	0.960	0.97 (0.75-0.97)	728 (21)		1395 (15)	1418 (16)	1475 (16)	5.36 (14)	11.3 (15)	5.24 (14)	1.91 (32)
0.72	2	8	1.44	1.97 (1.5-1.97)	611 (18)	482 (18)	1841 (13)	1890 (13)	1311 (13)	5.94 (22)	12.7 (13)	6.53 (22)	2.52 (36)
0.72	3	7	2.16	2.97 (2.97-2.97)	847 (8)	543 (20)	3353 (11)	3464 (11)	1605 (11)	6.47 (18)	10.4 (11)	5.82 (17)	2.29 (19)
0.54	4	6	2.16	4.00 (3.00-4.00)	539 (11)	361 (13)	2812 (6.5)	2862 (7.2)	1324 (7.2)	5.12 (19)	12.6 (7)	5.58 (14)	2.18 (12)
0.72/ 0.36	1/3	8	1.80	0.97 (0.97-0.97)	508 (13)		2445 (11)	2516 (12)	1398 (12)	5.86 (31)	11.9 (11)	6.05 (29)	2.06 (32)
All	1-4	24	All							5.61 (24)	11.9 (18)	5.76 (23)	2.17 (28)

^a Data are geometric mean values (% coefficient of variation) for each parameter except for T_{max} expressed as median values (range).

^b From 6 subjects.

**/assumption of a 60 Kg subject.

Subject 012 is not included in analysis of Cohort 2, Period 2 PK due to premature termination of infusion

Table 11B.
Mean Pharmacokinetic Parameters for N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-1-hydroxylamine Hydrogen Sulfate (XXXXVI)
in Human Plasma (GAL-021-102)^a

Infusion Rate (mg/kg/h)	Duration (h)	N	Dose (mg/kg)	T _{max} (h)	C _{max} (ng/mL)	C _{1H} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)	AUC _{0-∞} (ng·h/mL)	AUC _{0-∞} /D (mg·h/mL)	t _{1/2} (h)	CL _p (mL/min/kg)	V _z (L/kg)	V _{ss} (L/kg)
0.96	2	9	1.92	1.97 (1.50-2.00)	860 (23)	641 (27)	2595 (24)	2680 (25)	1397 (25)	6.81 (20)	11.9 (28)	7.04 (22)	2.48 (31)
1.44	2	8	2.88	1.97 (1.50-2.00)	1319 (22)	987 (20)	3828 (23)	3875 (23)	1345 (23)	5.15 (19)	12.4 (24)	5.53 (19)	1.79 (16)
1.92	2	7 ^b	3.84	1.97 (1.50-1.97)	1919 (14)	1250 (12)	5834 (14)	6058 (14)	1578 (14)	8.10 (6.5)	10.5 (15)	7.41 (10)	2.47 (14)
All	2	24	All							6.33 (24)	11.8 (25)	6.48 (22)	2.19 (29)

5

^a Data are geometric mean values (% coefficient of variation) for each parameter except for T_{max} expressed as median values (range).
^b From 4 subjects (Subjects 107 and 109 are not included in analysis due to premature termination of infusions).

During the second study, N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) was infused at 0.96, 1.44, and 1.92 mg/kg/h for 2-hours. In general, the plasma concentration-time profiles at higher doses were similar to those observed in the first-in-human study.

5 The mean maximum plasma concentrations ($C_{\max}$) were generally reached at the end of infusion as illustrated in Table 11B and Figure 44B. Following the end of infusion, all plasma concentration-time profiles displayed apparent bi-exponential decay with a steep distributional phase and a gradual terminal phase with a mean terminal half-life ($t_{1/2}$) ranging from 5.2 to 8.1 h.

10 Similar to those observed in the first-in-human study, the mean systemic plasma clearance values (CL_p), ranging from 10.5 to 12.4 ml/min/kg, were approximately half the hepatic blood flow rate in humans. The mean steady-state volume of distribution values (V_{ss}), ranging from 1.8 to 2.5 L/kg, were roughly 2-3 times the total body water in humans.

15 In general, N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) demonstrated well-behaved pharmacokinetics when administered intravenously to healthy volunteers in the dose range studied. The plasma concentration-time profiles fit well to a two-compartmental model with a short distributional half-life of less than 20 min. With
20 $C_{\max}$ and $AUC_{0-\infty}$ being dose-proportional and $t_{1/2}$, CL_p , and V_{ss} being dose-independent in the first study (0.1 – 0.96 mg/kg/h), without obvious deviation from predicted linearity during the second study. Future dosage regimen adjustments could be simplified as a result of the linear pharmacokinetics. The terminal half-life ($t_{1/2}$ ~6 h) suggest that little accumulation would occur after 24 hours, which is consistent
25 with low measurable plasma C_{24h} .

(d) Overall Conclusions from Phase I Clinical Trial(s)

N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) was well tolerated during the initial clinical study with only the sensation of mild/moderate burning at the site of infusion
30 being different from placebo. Minute ventilation increased at the two highest infusion rates (0.72 and 0.96 mg/kg/h). During the second study, hyperventilation occurred at the high dose (1.92 mg/kg/h) to establish a PD maximum dose in healthy subject untreated with respiratory depressive agents. The stimulation of minute ventilation was similar in the two studies at the 0.96 mg/kg/h infusion rate (~16%) with greater

stimulation at the high dose (25%). The drug was well behaved pharmacokinetically with a rapid concentration rise during the initial infusion period and rapid decline with cessation of the infusion. The compound is dose proportional for both AUC and C_{1h} with low inter- and intra-subject variability.

- 5 In the presence of opioid-induced respiratory depression, N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) administration was equally well tolerated compared to placebo with only mild burning sensation at infusion site in a few subjects. In the presence of clamped hypercapnia, minute ventilation, tidal volume and respiratory rate were increased to a statistically and clinically significant extent with (XXXVI) dose of 1.1 mg/kg/h. When breathing room air, similar ventilatory improvements were noted for minute ventilation, end-tidal CO₂, and tidal volume. Overall N-(4,6-*bis-n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine hydrogen sulfate (XXXVI) has useful pharmacology in a setting simulation the postoperative setting and has potential clinical utility in post-surgical respiratory depression.
- 10
- 15

Example 129

Development of Liquid Formulation for (XXXVI)

20 A. Solubility of (XXXV) as a function of pH

Methodology

- A solution of (XXXVI) of concentration $\sim 10^7$ mg/mL in 100 mM citric acid at pH 2.5 was prepared. About 150 μ L aliquots of this solution were transferred into 6 separate glass HPLC vials. Each aliquot was titrated with 6N sodium hydroxide to different pH values in the range 3-5.5 (Table 12A). All the samples, including the solution at pH 2.5, were shaken overnight at room temperature using a gyratory shaker. After shaking, the samples were evaluated visually for the presence of precipitate and were then spin filtered through 0.45 μ m syringe tip filters (4mm diameter) at 3,000 rpm for 20 min. The final pH values of the filtrates were measured. The filtrates were then diluted appropriately and analyzed for (XXXV) concentration using the HPLC assay.
- 25
- 30

Results

The pH values of the samples prior to and after shaking overnight, appearance as well as (XXXV) concentrations of samples are illustrated in Table 12A.

Solutions prepared at target pH values of 2.5, 3.0 and 3.5 were clear (no excess solid present) and hence the (XXXV) concentration values for these samples do not represent saturation solubility values. The pH solubility profile is shown in Figure 19B. The closed diamonds are saturation solubility values and open diamonds are measured concentrations in non-saturated samples (no excess solid present). The dotted line represents the best fit curve, which was plotted using Equation 1. This equation is a simplified representation of solubility equilibrium for weak bases that assumes that total solubility is much larger than the solubility of the free base in the pH range of interest:

$$\log S = \log S_0 + \log (1 + 10^{pK_a - pH}) \quad \text{Equation 1}$$

where, 'S' is total solubility; 'S₀' is the solubility of the free base.

Using the Microsoft Excel Solver function and a pK_a value of 5.6 for (XXXVI), Equation 1 was fit to the experimentally determined pH-solubility profile. The solubility value of free base thus calculated was 0.18 mg/mL. Based on this equation, solubility (expressed as the free base) is predicted to be 10 mg/mL at about pH 3.86, 25 mg/mL at about pH 3.46, and 50 mg/mL at about pH 3.16.

Table 12A. pH Solubility Results

target pH	initial pH	final pH after Shaking and Filtration	appearance afterwards Shaking	(XXXVI) concentration
2.5	2.51	2.42	Clear solution	104.1
3.0	3.05	3.00	Clear solution	99.8
3.5	3.51	3.51	Clear solution	101.6
4.0	4.00	3.79	Precipitate	20.8
4.5	4.55	4.37	Precipitate	3.46
5.0	4.93	4.52	Precipitate	2.73
5.5	5.63	5.02	Precipitate	0.99

20 B. Stability of (XXXV) as a Function of pH

Methodology

Buffer solutions containing ca. 10mM each of citric acid and glycine in the pH range 2-6 were prepared by titrating 250mL of a single stock containing both buffer agents with 1N NaOH/1N HCl and removing 50mL aliquots at predetermined pH values. XXXVI solutions at 1mg/mL were prepared in buffers of pH 2-5 by dissolving ~25mg of XXXVI in ~23mL of a given buffer, adjusting the pH to the target and making up the volume to 25.0 mL in a volumetric flask. (XXXVI) solution

at pH 6 was prepared similarly, but at a lower drug concentration of 0.25 mg/mL using 6.68 mg of (XXXVI).

Each of the buffered XXXV solutions was filtered through a 0.2µm polyether sulfone syringe filter into a volumetric flask, which had been previously rinsed with 70% ethanol and dried in a laminar flow hood. Following filtration, each buffered (XXXV) solution was split into 10 aliquots (9 aliquots of 2.5 mL each and 1 aliquot of 2 mL) in 5 mL serum vials previously rinsed with 70% ethanol and dried in a laminar flow hood. Filtration and preparation of aliquots were performed in a laminar flow hood. The 2 mL aliquot of each buffered (XXXV) solution was submitted for T0 analysis (HPLC assay and related substances).

Of the nine 2.5mL aliquots, three aliquots were stored at each 40 °C and 60 °C, two aliquots were stored at 25°C and one aliquot was stored at -70°C. Samples stored at 40°C and at 60°C were evaluated for physical appearance, pH, assay and related substances after 1 week, 2 weeks and 4 weeks of storage. Samples at 25°C and -70°C served as controls to be analyzed if necessary.

Results

The pH stability data are shown in Table 12B. All samples remained clear, colorless and particle free for up to 4 weeks of storage at both 40 °C and at 60 °C. The pH values for all the samples remained relatively constant for up to 4 weeks at both storage temperatures. Both the assay and impurities data indicate that (XXXV) is significantly less stable at pH 2 as compared to the remaining pH values evaluated. No specific trends were observed in the pH range 3-6. The pH stability profiles at 60 °C are shown in Figure 20A (% impurities).

Table 12B. pH Stability of (XXXV) (GAL 021) at pH 2-5

Test	Target pH	initial	40°C Storage			60°C Storage		
			1 wk	2 wk	4 wk	1 wk	2 wk	4 wk
pH	2	1.96	2.02	1.98	2.00	2.00	1.99	2.01
	3	3.02	3.05	3.05	3.06	3.07	3.03	3.07
	4	4.00	3.94	3.96	3.96	3.94	3.96	3.97
	5	5.03	4.90	4.95	4.97	4.92	4.93	4.98
	6	6.05	5.88	6.02	5.98	5.87	6.03	6.01
Assay	2	1.02	0.997	0.975	0.970	0.929	0.754	0.754

	3	0.984	0.984	0.987	0.991	0.971	0.952	0.952
	4	1.01	0.999	1.006	1.012	0.992	0.979	0.979
	5	1.01	0.989	0.992	0.977	0.977	0.947	0.947
	6	0.260	0.257	0.253	0.251	0.247	0.234	0.234
Impurities	2	n.d.	0.58	1.48	2.49	3.83	9.89	14.34
	3	n.d.	n.d.	0.19	0.41	0.71	1.20	2.19
	4	n.d.	n.d.	0.17	0.22	n.d.	0.52	1.02
	5	n.d.	n.d.	0.26	n.d.	n.d.	0.62	1.10
	6	n.d.	n.d.	0.25	0.28	0.56	0.87	1.65

n.d. = not detected

C. Stability of (XXXV) Across Narrow pH (pH 2-3.6)

Methodology

- 5 Buffer solutions containing ca.10mM each of citric acid and glycine in the pH range 2-3.6 were prepared by titrating 250mL of a single stock containing both buffer agents with 1N NaOH/1N HCl and removing 50mL aliquots at predetermined pH values. (XXXVI) solutions at 1mg/mL were prepared in the buffers by dissolving ~25mg of (XXXVI) in ca. 23mL of a given buffer, adjusting the pH to the target and
- 10 making up the volume to 25.0mL in a volumetric flask. Each of the buffered (XXXV) solutions was filtered through a 0.2µm polyether sulfone syringe filter into a volumetric flask previously rinsed with 70% ethanol and dried in a laminar flow hood. Following filtration, each buffered (XXXV) solution was split into 9 aliquots in 5mL serum vials previously rinsed with 70% ethanol and dried in a laminar flow hood.
- 15 Filtration and preparation of aliquots were performed in a laminar flow hood. Of the nine aliquots, three aliquots were stored at each 40 °C and 60 °C, two aliquots were stored at 25 °C and one aliquot was submitted for T0 testing. Samples were evaluated for pH, assay and related substances at T0 and, following 1 week, 2 weeks and 4 weeks of storage at 40 °C and 60 °C. Samples stored at 25°C served as controls to be
- 20 analyzed if necessary

Results

Data are summarized in Table 12C and in Figure 20B. The most notable result from this study is that during both 40 °C and 60 °C storage, impurity levels decreased significantly with increasing pH across the full pH range studied.

This means that any increase in the pH of the formulation led to an improvement in stability within the pH range in which an aqueous formulation is feasible.

Table 12C. pH Stability of (XXXV) at pH 2-3.6

Test	Target	initial	40°C Storage			60°C Storage		
			1 wk	2 wk	4 wk	1 wk	2 wk	4 wk
pH	2.0	2.00	2.00	1.98	1.98	2.00	1.97	1.89
	2.3	2.33	2.36	2.32	2.33	2.36	2.34	2.28
	2.7	2.72	2.73	2.72	2.73	2.75	2.74	2.67
	3.0	3.02	3.04	3.05	3.04	3.05	3.04	3.00
	3.3	3.31	3.35	3.35	3.34	3.36	3.37	3.34
	3.6	3.62	3.64	3.70	3.64	3.65	3.70	3.64
Assay	2.0	0.981	0.959	0.955	0.956	0.913	0.851	0.768
	2.3	0.987	0.984	0.993	0.995	0.961	0.932	0.916
	2.7	0.987	0.981	0.985	1.019	0.978	1.144	0.987
	3.0	1.005	1.01	0.987	1.027	0.991	0.975	0.987
	3.3	1.019	1.02	1.01	1.047	0.997	0.995	1.027
	3.6	0.996	0.991	0.985	0.991	0.979	0.958	0.979
Impurities	2.0	0.14	0.99	1.55	2.84	3.87	7.56	13.99
	2.3	0.09	0.47	0.63	1.70	1.81	3.53	6.30
	2.7	n.d.	0.22	0.37	0.61	0.97	1.76	3.09
	3.0	n.d.	0.21	0.34	0.58	0.61	1.27	1.82
	3.3	n.d.	n.d	n.d	0.25	0.41	0.69	1.26
	3.6	0.12	n.d	n.d	0.17	0.36	0.62	0.99

5

n.d. = not detected

D. Evaluation of the Solubility of (XXXV) in Solvents and IV Solutions

Methodology

The solubility of (XXXVI) and XXXV was evaluated in various
 10 solvents and IV solutions. The solvents and target concentration for solubility
 evaluation are shown in Table 12D. Due to limits on the API supply at the time the
 study was conducted, most of the solvent systems were evaluated to a level of only
 100 mg/mL even if the solution was not saturated at this level. Only in water was an
 attempt made to reach saturation solubility, regardless of how high that solubility
 15 might be. Solubility of the salt/free base in each solvent was evaluated in duplicate.

Evaluation of solubility of (XXXVI) in 0.9% NaCl, 5% dextrose,
 ethanol, 30% PEG 400, 70% PEG 400 and 100% PEG 400 was carried out at a target
 of 200mg/mL by adding ~100mg of drug to 500μL of solvent. The rest of the

solubility evaluations, except water, were carried out by adding ~50mg of drug (XXXVI or XXXV) to 500µL of solvent. For solubility in water, drug was added with intermittent shaking to ensure that excess undissolved drug is present indicating saturation 13 mm PTFE 0.2µm syringe filters. The filtrates were diluted appropriately
5 and analyzed for (XXXV) concentration by HPLC.

Results

The solubility results are shown in Table 12D.

(XXXVI): The solubility of (XXXVI) was greater than 400 mg/mL in water and at least 200 mg/mL in IV solutions (0.9% saline and 5% dextrose). During the
10 evaluation of solubility of the (XXXV) salt in water it was noted that ~350-400 mg the API dissolved completely in 500µL of water; however, the sample formed a cloudy gel following ca. 2h of shaking at room temperature that dissolved upon addition of water (~80-250µL). Further shaking of this clear solution overnight at room temperature resulted in a cloudy gel formation. Addition of another small
15 aliquot of water (~60-220µL) resulted in a fluid suspension that could be filtered and analyzed for (XXXV) concentration. The exact reason for this behavior of the (XXXVI) in water was not clear but may suggest formation of a supersaturated solution. The salt was also freely soluble in ethanol and methanol and had a saturation solubility of about 68 mg/mL in acetonitrile. The solubility in 30%, 70%
20 and 100% propylene glycol was at least 90 mg/mL. The solubility in 100% PEG-400 reached saturation at ca. 36 mg/mL but (XXXVI) was soluble to at least 90 mg/mL in 70% PEG-400 and ~198 mg/mL in 30% PEG-400.

(XXXV): The saturation solubility of (XXV) in water was ca. 0.21mg/mL, which is in agreement with the predicted value from the pH-solubility curve detailed
25 in Example 129A. The solubility in ethanol, methanol and acetonitrile were ~92mg/mL, ~102mg/mL and ~45mg/mL, respectively. The solubility of the free base in 5% Tween 80 dispersed system was ca. 2.7mg/mL. The solubility in PEG-400 and propylene glycol systems appears to increase with increasing levels of the cosolvent. The free base was more soluble in propylene glycol (~90mg/mL) than in PEG-400
30 (~73mg/mL). The data suggest that the solubility of XXXV free base in propylene glycol systems would be greater than in PEG-400 systems at similar pH values.

Table 12D. Solubility of (XXXV) in Solvents and IV Solutions

Solvent System	Replicate	(XXXV) hydrogen sulfate salt			(XXXV) free base		
		pH	Solubility (mg/mL)	Saturation Solubility	pH	Solubility (mg/mL)	Saturation Solubility
Water	1	0.40	414.5	Y	8.80	0.206	Y
	2	0.31	441.5	Y	8.67	0.206	Y
0.9% NaCl	1	0.61	>206.2	N	Not determined		
	2	0.62	>201.4	N			
5% Dextrose	1	0.61	>201.2	N	Not determined		
	2	sample not recoverable					
Ethanol	1	NA	>211.4	N	NA	96.04	Y
	2	NA	>212.2	N	NA	87.24	Y
30% PEG-400	1	0.84	>197.0	N	4.30	17.03	Y
	2	0.82	>198.4	N	4.35	17.30	Y
70% PEG-400	1	1.68	>85.28	N	5.98	14.78	Y
	2	1.65	>91.43	N	6.09	11.76	Y
PEG-400	1	NA	35.74	Y	NA	68.3	Y
	2	sample not recoverable			NA	77.8	Y
30% Propylene Glycol	1	1.06	>93.21	N	7.36	0.87	Y
	2	1.07	>89.47	N	7.51	0.84	Y
70% Propylene Glycol	1	1.22	>87.80	N	7.93	12.4	Y
	2	1.18	>92.43	N	8.25	12.1	Y
Propylene Glycol	1	NA	>92.09	N	NA	87.0	Y
	2	NA	>94.65	N	NA	93.2	Y
Methanol	1	NA	>108.9	N	NA	94.82	Y
	2	NA	>98.52	N	NA	108.38	Y
Acetonitrile	1	NA	68.5	Y	NA	49.4	Y
	2	NA	67.1	Y	NA	39.9	Y
5% Tween 80	1	Not determined			7.54	2.69	Y
	2				7.61	2.68	Y

* NA = not applicable. Samples listed as not recoverable were lost due to filtration failures.

E. Stability of (XXXV) as a Function of Buffer Strength

5 Methodology

A 10mg/mL (XXXVI) solution in 100 mM citrate buffer at pH 3.0 and a 500mM citrate buffer at pH 3.0 were prepared. Using these two stock solutions, (XXXVI) solutions at 1mg/mL were prepared in citrate buffers of various concentrations in the range 10-250mM, as shown in Table 12E.

Table 12E. Solutions for Evaluation of Stability as a Function of Buffer Strength

Solution	Volume of 10 mg/mL (XXXV) in 100mM citrate pH 3.0 (mL)	Volume of 500 mM Citrate pH 3.0 (mL)	Volume of Water (mL)
1mg/mL (XXXV) in 10mM Citrate	2	0	QS to 20.0mL
1mg/mL(XXXV) in 20mM Citrate	2	0.4	QS to 20.0mL
1mg/mL (XXXV) in 50mM Citrate	2	1.6	QS to 20.0mL
1mg/mL (XXXV) in 100mM Citrate	2	3.6	QS to 20.0mL
1mg/mL (XXXV) in 250mM Citrate	2	9.6	QS to 20.0mL

- Each of the above solutions was stored in 5mL serum vials as ca. 2.5-3mL aliquots (total of 7 aliquots). Two aliquots were stored at each of 40 °C, 60 °C and 25 °C. Aliquots stored at 25 °C served as control s to be evaluated if necessary. At T0 and after 2 weeks of storage at 40 °C and at 60 °C, samples were evaluated for pH, assay and related substances.

Results

- Data from the buffer effect study are summarized in Table 12F. Impurity levels increased noticeably at the highest buffer concentration, but there was no effect of buffer strength at 40 °C within the range of buffer concentration relevant to the formulation.

Table 12F. Effect of Buffer Strength on (XXXV) Stability

Test	Buffer Strength	initial	40°C Storage		60°C Storage	
			1 wk	2 wk	1 wk	2 wk
pH	10 mM	3.16	3.26	3.21	3.3	3.2
	20 mM	3.27	3.33	3.30	3.3	3.3
	50 mM	3.28	3.34	3.29	3.3	3.3
	100 mM	3.30	3.32	3.29	3.3	3.2
	250 mM	3.21	3.25	3.22	3.2	3.2
Assay	10 mM	0.971	0.953	0.947	0.953	0.956
	20 mM	1.01	0.965	0.966	0.943	0.947
	50 mM	0.976	0.959	0.949	0.936	0.943
	100 mM	0.962	0.964	0.956	0.962	0.946
	250 mM	0.947	0.972	0.945	0.955	0.936
	10 mM	n.d.	n.d.	n.d.	0.48	0.89

Impurities	20 mM	n.d.	0.13	n.d.	0.58	0.88
	50 mM	n.d.	n.d.	n.d.	0.59	0.87
	100 mM	n.d.	0.26	0.38	0.73	1.20
	250 mM	n.d.	0.21	0.56	1.03	1.80

n.d. = not detected

F. Prototype Formulations

Methodology

5 A total of nine (XXXV) prototypes were prepared that included a simple buffered solution, co-solvent systems as well as non-aqueous solutions. These are shown in Table 12G. Prototypes 6, 7 and 8 resulted in significant precipitation during preparation and hence were not evaluated further. The remaining prototypes were stored at 2-8 °C, room temperature, 40 °C and 60 °C in serum vials. Samples
10 stored at 2-8 °C and room temperature were analyzed at selected timepoints.

Results

Data gathered to date are provided in Table 12G.1-12G.6. The aqueous buffered formulation (Prototype #1) has been found to be stable at room temperature and under refrigeration, but some degradation has been observed under
15 accelerated conditions. Of special concern is that a very small amount of precipitate, described as one or two snowflake-like particles, has been observed after 2 weeks at 60 °C and after 8 weeks at 40 °C. Since the appearance of this precipitate during 60 °C storage coincided with an actual decrease in the primary impurity peak, the possibility of the degradant being insoluble is under investigation.

20 (XXXV) was unstable in Prototype #2, 50% PEG/50% water without pH adjustment. The instability was presumably due to the low pH of this formulation. The drug was found to be much more stable in Prototype #3, which has the same 50% PEG base but also contains sufficient sodium hydroxide to bring the apparent pH up to about 4.5. Similarly, good stability was seen in Prototype #9, 70% propylene
25 glycol/30% water with ammonium acetate buffer to bring the apparent pH to about 5.3. Good stability was also seen in simple solutions of the salt in PEG or propylene glycol, presumably due to the absence of water as a reactant.

Table 12G. (XXXVI) Prototypes for Stability Evaluation

Prototype #	Description
1	35 mg/mL (XXXV).H ₂ SO ₄ in 50mM citrate, pH 3.0
2	35 mg/mL (XXXV).H ₂ SO ₄ in 50% v/v PEG-400 in water
3	35 mg/mL (XXXV).H ₂ SO ₄ in 50% v/v PEG-400 in water adjusted to pH 4.4 with 1N NaOH
4	30 mg/mL (XXXV).H ₂ SO ₄ in 100% PEG-400
5	35 mg/mL (XXXV).H ₂ SO ₄ in 100% propylene glycol
6	35 mg/mL (XXXV).H ₂ SO ₄ in 50% v/v PEG-400 in acetate solution (~40mM sodium acetate and ~100mM sodium hydroxide)
7	35 mg/mL (XXXV).H ₂ SO ₄ in 50% v/v propylene glycol in acetate solution (~40mM sodium acetate and ~100mM sodium hydroxide)
8	35 mg/mL (XXXV).H ₂ SO ₄ in 50% v/v PEG-400 in acetate solution (~40mM ammonium acetate and ~100mM ammonium hydroxide)
9	35 mg/mL (XXXV).H ₂ SO ₄ in 70% v/v propylene glycol in acetate solution (~40mM ammonium acetate and ~100mM ammonium hydroxide)

Table 12G.1. Stability of (XXXV) Formulation Prototype #1

Formulation #1:					
35mg/mL (XXXV).H ₂ SO ₄ in 50mM citrate, pH 3.0					
Parameter	Temperature	Initial	1 week	2 weeks	4 weeks
pH	2-8°C	2.97	3.04	--	--
	RT		3.04	--	3.07
	40°C		2.99	3.01	3.06
	60°C		3.01	3.02	2.97
Assay	2-8°C	35.73	36.22	NA	NA
	RT		35.93	--	35.31
	40°C		34.83	35.40	33.96
	60°C		37.90	34.63	31.89
Impurities	2-8°C	n.d.	n.d.	--	--
	RT		n.d.	--	n.d.
	40°C		n.d.	0.35	0.52
	60°C		0.73	0.49	0.51

5

Table 12G.2. Stability of (XXXV) Formulation Prototype #2

Formulation #2:					
35mg/mL (XXXV).H ₂ SO ₄ in 50% v/v PEG-400 in water					
Parameter	Temperature	Initial	1 week	2 weeks	4 weeks

pH	RT	2.00	2.01	NA	2.07
	40°C		2.04	2.03	2.11
	60°C		2.04	2.14	2.36
Assay	RT	33.93	35.26	NA	34.47
	40°C		35.30	34.81	33.92
	60°C		33.70	31.77	27.45
Impurities	RT	n.d.	0.39	0.39	1.10
	40°C		0.92	0.92	2.53
	60°C		2.11	2.11	11.99

Table 12G.3. Stability of (XXXV) Formulation Prototype #3

Formulation #3: 35mg/mL (XXXV).H ₂ SO ₄ in 50% v/v PEG-400 in water adjusted to pH 4.4 with 1N					
Parameter	Temperature	Initial	1 week	2 weeks	4 weeks
pH	2-8°C	4.38	4.51	NA	NA
	R		4.40	NA	4.52
	40°		4.20	4.43	4.41
	60°		4.16-3.88	4.22	4.27
Assay	2-8°C	22.17	37.31	NA	NA
	R		36.23	NA	36.03
	40°		35.66	36.53	35.96
	60°		35.33	34.70	34.14
Impurities	2-8°C	n.d.	n.d.	NA	NA
	R		n.d.	NA	n.d.
	40°		n.d.	n.d.	0.90
	60°		0.62	1.50	1.91

Table 12G.4. Stability of (XXXV) Formulation Prototype #4

Formulation #4: 30mg/mL (XXXV).H ₂ SO ₄ in 100% PEG-400					
Parameter	Temperature	Initial	1 week	2 weeks	4 weeks
Assay	2-8°C	27.94	30.18	NA	NA
	RT		30.20	NA	30.31
	40°C		29.91	29.89	30.19
	60°C		29.24	29.60	29.97
Impurities	2-8°C	n.d.	n.d.	NA	NA
	RT		n.d.	NA	n.d.
	40°C		n.d.	n.d.	n.d.
	60°C		0.50	0.50	0.37

Table 12G.5. Stability of (XXXV) Formulation Prototype #5

Formulation #5: 35mg/mL (XXXV).H ₂ SO ₄ in 100% propylene glycol					
Parameter	Temperature	Initial	1 week	2 weeks	4 weeks
Assay	2-8°C	28.97	36.22	NA	NA
	RT		36.23	NA	36.00
	40°C		35.16	35.63	36.03
	60°C		35.56	35.33	35.56
Impurities	2-8°C	n.d.	n.d.	NA	NA
	RT		n.d.	NA	n.d.
	40°C		n.d.	0.12	0.27
	60°C		0.23	0.74	0.99

Table 12G.6. Stability of (XXXV) Formulation Prototype #9

Formulation #9: 35mg/mL (XXXV).H ₂ SO ₄ in 70% v/v propylene glycol in acetate solution (~40mM)					
Parameter	Temperature	Initial	1 week	2 weeks	4 weeks
pH	2-8°C	5.28	5.27	NA	
	RT		NA	NA	
	40°C		5.26	5.35	
	60°C		5.25	5.34	
Assay	2-8°C	35.50	34.40	NA	
	RT		NA	NA	
	40°C		34.36	34.62	
	60°C		34.69	34.55	
Impurities	2-8°C	n.d.	n.d.	NA	
	RT		NA	NA	
	40°C		n.d.	n.d.	
	60°C		n.d.	0.39	

5 G. Final Formulation and GMP Drug Product Stability Data

The final formulation is shown in Table 12H. Stability data for drug product formulation in accord with Table 12H are shown in Table 12I.1 and 12I.2 at 25 °C/60 %RH and 2-8°C, respectively. The levels of N-(4,6-Bis(propylamino)-1,3,5-triazin-2-ol (CLXXVIII) measured during the stability study are shown in Table

10 12J.

Table 12H. Final Formulation for (XXXV)

Component	Function	Concentration	% w/w
(XXXV)	Active	10 mg/mL (as free base)	1.386 (as salt)
Citric acid, Anhydrous, USP	Buffer	20 mM	0.384
1 N Sodium Hydroxide	adjust pH to 3.2	q.s.	q.s.
Sterile Water for Injection, USP	solvent	q.s.	q.s.

Table 12I.1. Long-term stability results (25°C/60%RH) for Formulated (XXXVI),
GMP lot# 041I0511^a

Test	Specification	Months					
		0	1 (I)*	3 (I)*	6 (I)*	6 (U)**	9 (I)*
Appearance of Solution	b.	(3) ^b	(2) ^b	(2) ^b	(2) ^b	(2) ^b	(2) ^b
pH	2.7-3.6	(3) 3.1, 3.1, 3.1	(2) 3.1, 3.1	(2) 3.1, 3.1	(2) 3.1, 3.2	(2) 3.1, 3.2	3.1, 3.1
Osmolality	Report Results, mOsm/kg	(3) 126, 126, 127	(2) 125, 125	2) 128, 128	2) 127, 127	2) 127, 128	125,125
Vial Appearance	d.	(2) ^c	(2) ^c	(2) ^c	(2) ^c	(2) ^c	(2) ^c
Identification by Retention Time	Retention time between 0.98 and 1.02 relative to standard	(3) 0.99, 0.99, 0.99	(2) 1.00 1.00	(2) 1.00, 1.00	(2) 1.00, 1.00	(2) 1.00, 1.00	1.00 1.00
Assay	90 – 110% of label claim	(3) 99.1, 99.1, 99.3	(2) 97.9%, 97.9%	(2) 97.5%, 98.1%	(2) 99.3%, 97.4%	(2) 98.2%, 98.3	(2) 96.2%, 96.2%
Related Substances	NMT 1.00% for any single related substance NMT 3.00% total related substances	(3) <0.10% <0.10% <0.10% Totals <0.10 all	(2) RRT 0.672: 0.15% RRT 0.672: 0.15% Total: 0.15 Total: 0.15	2) RRT 0.672: 0.44% RRT 0.672: 0.44% Total: 0.44	2) RRT 0.672: 0.82% RRT 0.672: 0.82% Total: 0.82	2) RRT 0.672: 0.81% RRT 0.672: 0.81% Total: 0.81%	RRT 0.672: 1.16 RRT 0.672: 1.16 Total: 1.16 Total: 1.16
Subvisible Particulates	f.	(3) 207, 37 122, 7 177, 0		(3) 418, 0 306, 0 282, 0	(3) 78, 0 99, 0 54, 0		
Weight Loss (5 vials)	NMT 2.5 g loss in weight		(5) 0.0 all	(5) 0.0 all			(5) 0.0 all

- a. Package components for GMP batch: 50 mL clear, 20 mm opening, USP Type 1 glass (Wheaton 223745); Gray butyl teflon 2 coated stoppered. 4416/50 (West 1014 4937); flip off seal, 20 mm, 3766 white, 8-bridge (West 5420 3028).
- b. Colorless to pale yellow liquid. Clear and particle free
- 5 c. Colorless liquid. Clear and particle free
- d. Vial free of cracks, stopper securely in place and no sign of leakage
- e. Both vials free from crack stoppers securely in place, no sign of leakage
- f. For each container: NMT 6000 $\geq$ 10 μ m particles; NMT 600 $\geq$ 25 μ m
- *(I) = inverted; ** (U) = upright

10

Table 12I.2. Long-term stability results (5°C/Ambient) for Formulated (XXXVI),
GMP lot# 041I0511^a

Test	Specification	Months						
		0	1(I)*	3 (I)*	6 (I)*	6 (U)**	9 (I)*	10
Appearance of Solution	b.	(2) ^b	(2) ^b	(2) ^b	(2) ^b	(2) ^b	(2) ^b	
pH	2.7-3.6	3.1, 3.1	(2) 3.1, 3.1	(2) 3.1, 3.1	(2) 3.1, 3.1	(2) 3.1, 3.1	(2) 3.1, 3.1	
Osmolality	Report Results mOsm/kg	(2) 124 124	(2) 124, 124	(2) 127, 127	(2) 128, 128	(2) 128, 128 kg	(2) 124, 124	
Vial Appearance	d.	(2) ^e	(2) ^e	(2) ^e	(2) ^e	(2) ^e	(2) ^e	
Identification by Retention Time	Retention time between 0.98 and 1.02 relative to standard	1.00 1.00	(2) 1.00 1.00	(2) 1.00 1.00	(2) 1.00 1.00	(2) 1.00 1.00	(2) 1.00 1.00	
Assay	90 – 110% of label claim	97.8, 97.8	(2) 98.3, 98.3	(2) 99.0, 99.0	(2) 100.1, 100.2	(2) 99.2, 99.2	(2) 97.8, 97.8	
Related Substances	NMT 1.00% for any single related substance NMT 3.00% total related substances	RRT 0.672: 0.11 RRT 0.672: 0.11 Total: 0.11 Total: 0.11	(2) <0.10%, <0.10% Total: <0.10%	(2) <0.10%, <0.10% Total: <0.10%	(2) <0.10%, <0.10% Total: <0.10%	(2) <0.10%, <0.10% Total: <0.10%	(2) RRT 0.672: 0.11 RRT 0.672: 0.11 Total: 0.11 Total: 0.11	
Subvisible Particulates	f.		(3) 224, 0 150, 0 71, 0	(3) 224, 0 150, 0 71, 0	(3) 27, 0 75, 0 139, 0	(3) 156, 0 150, 0 146, 0		(3) (I)* 133, 0 160, 0 68, 3
Weight Loss (5 vials)	NMT 2.5 g loss in weight	(5) 0.0 all	(5) 0.0 all	(5) 0.0 all	(5) 0.0 all	(5) 0.0 all	(5) 0.0 all	
LAL*	NMT 4EU/mL							(I) <0.5 EU/mL
Sterility*								

- a. Package components for GMP batch: 50 mL clear, 20 mm opening, USP Type 1 glass (Wheaton 223745); Gray butyl teflon 2 coated stopped. 4416/50 (West 1014 4937); flip off seal, 20 mm, 3766 white, 8-bridge (West 5420 3028).
- b. Colorless to pale yellow liquid. Clear and particle free
- 5 c. Colorless liquid. Clear and particle free
- d. Vial free of cracks, stopper securely in place and no sign of leakage
- e. Both Vials free from crack stoppers securely in place, no sign of leakage
- f. For each container: NMT 6000 $\geq$ 10 μ m particles; NMT 600 $\geq$ 25 μ m
- *(I) = inverted; ** (U) = upright

10

Table 12J.

Level of Degradant 4,6-Bis(propylamino)-1,3,5-triazin-2-ol (CLXXVIII)

GMP Stability Study, Lot # GMP lot# 041I0511

	Release Testing (Drug Product Production lot Sample Pull)			T = 1 month		T = 3 month		T = 6 month		T = 9 month	
	Beg.	Mid.	End	Vial 1	Vial 2	Vial 1	Vial 2	Vial 1	Vial 2	Vial 1	Vial 2
5°C, amb. RH Inverted	0.00	0.00	0.00	0.03	0.03	0.06	0.06	0.08	0.08	0.11	0.11
5°C, amb. RH Upright				NA	NA	NA	NA	0.08	0.08	NA	NA

- 15 The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety. While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the
- 20 invention. The appended claims are intended to be construed to include all such embodiments and equivalent variations.

CLAIMS

What is claimed is:

- 5 1. A composition comprising at least one compound selected from the group consisting of: N-(2,4-bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine (CLXXII), N-(2,4,6-tris-*n*-propylamino)-[1,3,5]triazine (CLXXIII), N-(2,4,6-tris-*n*-propylamino)-1,3-pyrimidine (CLXXIV), N-(2,4-bis-*n*-propylamino)-N-(6-*i*-propylamino)-1,3-pyrimidine (CLXXV), a salt thereof, and any combinations
10 thereof.
2. The composition of claim 1, wherein the salt is hydrogen sulfate, hydrochloride, phosphate, hydrogen phosphate or dihydrogen phosphate.
3. The composition of claim 1, further comprising at least one pharmaceutically acceptable carrier.
- 15 4. A method of preventing or treating a breathing control disorder or disease in a subject in need thereof, the method comprising administering to the subject an effective amount of a pharmaceutical formulation comprising at least one pharmaceutically acceptable carrier and at least one compound selected from the group consisting of: N-(2,4-bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine
20 (CLXXII), N-(2,4,6-tris-*n*-propylamino)-[1,3,5]triazine (CLXXIII), N-(2,4,6-tris-*n*-propylamino)-1,3-pyrimidine (CLXXIV), N-(2,4-bis-*n*-propylamino)-N-(6-*i*-propylamino)-1,3-pyrimidine (CLXXV), a salt thereof, and any combinations thereof.
5. The method of claim 4, wherein the breathing control disorder or disease is selected from the group consisting of respiratory depression, sleep apnea,
25 apnea of prematurity, obesity-hypoventilation syndrome, primary alveolar hypoventilation syndrome, dyspnea, hypoxia, and hypercapnia.
6. The method of claim 5, wherein the respiratory depression is caused by an anesthetic, a sedative, an anxiolytic agent, a hypnotic agent, alcohol or a narcotic.

7. The method of claim 4, wherein the subject is further administered a composition comprising at least one additional compound useful for treating the breathing control disorder or disease.

8. The method of claim 7, wherein the at least one additional compound is selected from the group consisting of acetazolamide, almitrine, theophylline, caffeine, methyl progesterone, a serotonergic modulator, a cannabinoid and an ampakine.

9. The method of claim 4, wherein the formulation is administered in conjunction with the use of a mechanical ventilation device or positive airway pressure device on the subject.

10. The method of claim 4, wherein the subject is a mammal.

11. The method of claim 10, wherein the mammal is a human.

12. The method of claim 4, wherein the formulation is administered to the subject by an inhalational, topical, oral, buccal, rectal, vaginal, intramuscular, subcutaneous, transdermal, intrathecal, intraperitoneal, intrathoracic, intrapleural or intravenous route.

13. A method of preventing destabilization or stabilizing breathing rhythm in a subject in need thereof, the method comprising administering to the subject an effective amount of a pharmaceutical formulation comprising at least one pharmaceutically acceptable carrier and at least one compound selected from the group consisting of: N-(2,4-bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine (CLXXII), N-(2,4,6-tris-*n*-propylamino)-[1,3,5]triazine (CLXXIII), N-(2,4,6-tris-*n*-propylamino)-1,3-pyrimidine (CLXXIV), N-(2,4-bis-*n*-propylamino)-N-(6-*i*-propylamino)-1,3-pyrimidine (CLXXV), a salt thereof, and any combinations thereof.

14. The method of claim 13, wherein the destabilization is associated with a breathing control disorder or disease selected from the group consisting of respiratory depression, sleep apnea, apnea of prematurity, obesity-hypoventilation syndrome, primary alveolar hypoventilation syndrome, dyspnea, hypoxia, and hypercapnia.

15. The method of claim 14, wherein the respiratory depression is caused by an anesthetic, a sedative, an anxiolytic agent, a hypnotic agent, alcohol or a narcotic.

16. The method of claim 15, wherein the subject is further
5 administered a composition comprising at least one additional compound useful for treating the breathing control disorder or disease.

17. The method of claim 16, wherein the at least one additional compound is selected from the group consisting of acetazolamide, almitrine, theophylline, caffeine, methyl progesterone, a serotonergic modulator, a cannabinoid
10 and an ampakine.

18. The method of claim 13, wherein the formulation is administered in conjunction with the use of a mechanical ventilation device or positive airway pressure device on the subject.

19. The method of claim 13, wherein the subject is a mammal.

15 20. The method of claim 19, wherein the mammal is a human.

21. The method of claim 13, wherein the formulation is administered to the subject by an inhalational, topical, oral, buccal, rectal, vaginal, intramuscular, subcutaneous, transdermal, intrathecal, intraperitoneal, intrathoracic, intrapleural or intravenous route.

20 22. A composition comprising N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV) or a salt thereof, wherein 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol (CLXXVIII) is present at a level equal to or lower than about 1% (w/w) with respect to (XXXV) or the salt thereof.

23. The composition of claim 22, wherein 4,6-bis-(*n*-propylamino)-
25 1,3,5-triazin-2-ol (CLXXVIII) is present at a level equal to or lower than about 0.5% (w/w) with respect to (XXXV) or the salt thereof.

24. The composition of claim 23, wherein 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol (CLXXVIII) is present at a level equal to or lower than about 0.3% (w/w) with respect to (XXXV) or the salt thereof.

25. The composition of claim 24, wherein 4,6-bis-(*n*-propylamino)-
5 1,3,5-triazin-2-ol (CLXXVIII) is present at a level equal to or lower than about 0.2% (w/w) with respect to (XXXV) or the salt thereof.

26. The composition of claim 25, wherein 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol (CLXXVIII) is present at a level equal to or lower than about 0.15% (w/w) with respect to (XXXV) or the salt thereof.

10 27. The composition of claim 26, wherein 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol (CLXXVIII) is present at a level equal to or lower than about 0.1% (w/w) with respect to (XXXV) or the salt thereof.

28. The composition of claim 27, wherein 4,6-bis-(*n*-propylamino)-1,3,5-triazin-2-ol (CLXXVIII) is essentially absent from the composition.

15 29. A composition comprising N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV) or a salt thereof, further comprising a buffer and a liquid carrier.

30. The composition of claim 29, wherein the salt of (XXXV) is the hydrogen sulfate salt (XXXVI).

20 31. The composition of claim 29, further comprising citric acid.

32. The composition of claim 29, wherein the pH of the composition is adjusted with a base.

33. The composition of claim 32, wherein the base comprises sodium hydroxide.

25 34. The composition of claim 29, wherein the liquid carrier comprises water.

35. The composition of claim 29, wherein the pH of the composition ranges from about 2.5 to about 6.

36. The composition of claim 35, wherein the pH of the composition ranges from about 2.5 to about 5.

5 37. The composition of claim 36, wherein the pH of the composition ranges from about 3 to about 4.

38. The composition of claim 29, wherein the concentration of (XXXV) or the salt thereof in the composition is about 1-10 mg/mL.

39. The composition of claim 38, wherein the concentration of
10 (XXXV) or the salt thereof in the composition is about 5-10 mg/mL.

40. The composition of claim 39, wherein the concentration of (XXXV) or the salt thereof in the composition is about 10 mg/mL.

41. The composition of claim 29, comprising less than 0.5% (w/w) (CLXXVIII) with respect to (XXXV).

15 42. The composition of claim 41, wherein less than 0.5% (w/w) of N-(4,6-Bis-n-propylamino)-[1,3,5]-triazin-2-ol (CLXXVIII) with respect to (XXXV) forms over a six-month period of storage of the composition at 2-8°C.

43. The composition of claim 42, wherein less than 0.5% (w/w) of N-(4,6-Bis-n-propylamino)-[1,3,5]-triazin-2-ol (CLXXVIII) with respect to (XXXV)
20 forms over a twelve-month period of storage of the composition at 2-8°C.

44. The composition of claim 43, wherein less than 0.5% (w/w) of N-(4,6-Bis-n-propylamino)-[1,3,5]-triazin-2-ol (CLXXVIII) with respect to (XXXV) forms over an eighteen-month period of storage of the composition at 2-8°C.

45. The composition of claim 44, wherein less than 0.5% (w/w) of
25 N-(4,6-Bis-n-propylamino)-[1,3,5]-triazin-2-ol (CLXXVIII) with respect to (XXXV) forms over a twenty-four-month period of storage of the composition at 2-8°C.

46. A crystalline free base of N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV), Form A, with a XRPD spectrum as per Figure 22.

47. At least one crystalline salt of N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV) selected from the group consisting of:
- (i) crystalline hydrogen sulfate salt (XXXVI) Form A, with a XRPD spectrum as per Figure 14;
 - (ii) crystalline hydrogen sulfate salt (XXXVI) comprising a mixture of Form A and Form B, with a XRPD spectrum as per Figure 23;
 - (iii) crystalline hydrogen sulfate salt (XXXVI) Form C, with a XRPD spectrum as per Figure 24;
 - (iv) crystalline hydrogen sulfate salt (XXXVI) Form D, with a XRPD spectrum as per Figure 25;
 - (v) crystalline hydrogen sulfate salt (XXXVI) comprising a mixture of Form A and Form D, with a XRPD spectrum as per Figure 26;
 - (vi) crystalline phosphoric acid salt (CLXXX) Form A, with a XRPD spectrum as per Figure 27;
 - (vii) crystalline phosphoric acid salt (CLXXX) Form C, with a XRPD spectrum as per Figure 28;
 - (viii) crystalline phosphoric acid salt (CLXXX) comprising a mixture of Form A and Form B, with a XRPD spectrum as per Figure 29;
 - (ix) crystalline phosphoric acid salt (CLXXX) comprising a mixture of Form C and Form D, with a XRPD spectrum as per Figure 30;
 - (x) crystalline phosphoric acid salt (CLXXX) comprising a mixture of Form C and Form E, with a XRPD spectrum as per Figure 31;
- and any mixtures thereof.

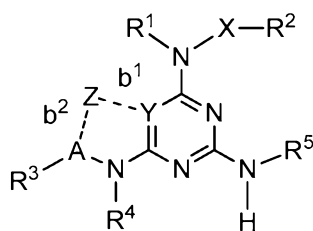
48. A salt of N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine (XXXV), comprising approximately one mole equivalent of sulfuric acid.

49. The salt of claim 48, further comprising one mole equivalent of water.

50. A salt of N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine (XXXV), comprising at least one mole equivalent of phosphoric acid.

51. The salt of claim 50, comprising about one mole equivalent of
5 phosphoric acid.

52. A method of reducing or minimizing the open channel fraction of the potassium maxi-K or BK channel in a subject in need thereof, the method comprising administering to the subject an effective amount of a pharmaceutical formulation comprising at least one pharmaceutically acceptable carrier and at least
10 one compound of formula (I):



(I), wherein

R^1 and R^2 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl; or R^1
15 and R^2 combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

R^3 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-NR^1R^2$, $-C(O)OR^1$, acyl, or aryl;
20

R^4 is H, alkyl, or substituted alkyl;

R^5 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-OR^1$, $-NR^1R^2$, $-C(O)OR^1$, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, or substituted heterocyclic; or R^3 and R^5 combine
25 as to form a biradical selected from the group consisting of 3,6,9-trioxa-undecane-1,11-diyl and 3,6-dioxa-octane-1,8-diyl;

R^6 is H, alkyl, substituted alkyl or alkenyl;

X is a bond, O or NR^4 ; and,

Y is N, CR⁶ or C; wherein:

if Y is N or CR⁶, then bond b¹ is nil and:

(i) Z is H, bond b² is a single bond, and A is CH; or,

(ii) Z is nil, bond b² is nil, and A is a single bond;

5 and,

if Y is C, then bond b¹ is a single bond, and:

(i) Z is CH₂, bond b² is a single bond, and A is CH; or,

(ii) Z is CH, bond b² is a double bond, and A is C;

or a salt thereof.

10 53. The method of claim 52, wherein the compound of formula (I) is selected from the group consisting of: N-(4,6-Bis-methylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-ethylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-Cyclopropylmethyl)-N-(6-*n*-propylamino) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-Ethylamino)-N-(6-*n*-
15 propylamino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2-methylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2,2-dimethylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2,2-dimethylpropylamino))[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-
20 hydroxylamine, N-(4-(Methoxy(methyl)amino)-6-(*n*-propylamino)-1,3,5-triazin-2-yl)propionamide, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-methyl-hydroxylamine, O-Allyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine, 6-(Methoxy(methyl)amino)-N²-propyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-
25 propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine, O-Benzyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-isopropyl-hydroxylamine, 6-[1,2]Oxazinan-2-yl-N,N'-dipropyl-[1,3,5]triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-N-methyl-hydroxylamine, O-Benzyl-N-(4,6-bis-*n*-propylamino-
30 [1,3,5]triazin-2-yl)-N-ethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-hydroxylamine, 6-((Benzyloxy)(isopropyl) amino)-N²,N⁴-dipropyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-O-isopropyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isobutyl-

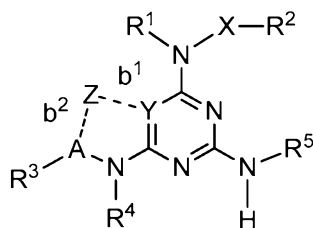
N-methyl-hydroxylamine, 6-(Methyl(thiophen-2-ylmethoxy)amino)-N²,N⁴-dipropyl-
 1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-
 cyclopropylmethyl-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-
 [1,3,5]triazin-2-yl)-O-ethyl-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-
 5 [1,3,5]triazin-2-yl)-O-(2,2-difluoro-ethyl)-hydroxylamine, 4-N-(2-
 Dimethylaminoethyl)amino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-
 hydroxylamine, 4-N-(3-(1-N-Methylimidazol-2-yl)-propyl)-amino-6-N-(*n*-
 propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4-N-(1-N-
 Methylimidazol-2-yl)-methylamino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-
 10 dimethyl-hydroxylamine, 4,6-Bis-(N-(2-dimethylaminoethyl)amino)-[1,3,5]triazin-2-
 yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-(N-(pyridin-4-yl-methyl)amino)-
 [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-[N-(3-methoxy-*n*-
 propyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-[N-
 (tetrahydropyran-4-yl-methyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-
 15 hydroxylamine, N-(5,8,11-Trioxa-2,14,16,18,19-pentaazabicyclo[13.3.1]nonadeca-
 1(18),15(19),16(17)-trien-17-yl)-N,O-dimethylhydroxylamine, 2,6-Bis-(N-*n*-
 propylamino)-[1,3]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-*n*-
 propylamino-[1,3,5]triazin-2-yl)-N',N'-dimethylhydrazine, N-(4,6-Bis-*n*-
 propylamino-[1,3,5]triazin-2-yl)-N-methyl-N'-methylhydrazine, 2-(*n*-Propyl)amino-
 20 4-(*i*-propylamino-7-methyl-pyrrolidino[2,3-*d*]pyrimidine, 2-(*n*-Propyl)amino-4-
 dimethylamino-7-methyl-pyrrolidino[2,3-*d*]pyrimidine, 2-(*n*-Propyl)amino-4-
 methylamino-7-methyl-pyrrolidino[2,3-*d*]pyrimidine, 2-(*n*-Propyl)amino-4-(*i*-
 propyl)amino-7-*i*-propyl-pyrrolidino[2,3-*d*]pyrimidine, 2,4-Bis-(*n*-propyl)amino-7H-
 pyrrolidino[2,3-*d*]pyrimidine, 2-(*n*-Propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-
 25 methyl-pyrrolidino[2,3-*d*]pyrimidine, 8-(7-Methyl-2-(*n*-propylamino)-
 pyrrolidino[2,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol, N-(2-Propylamino-
 7H-pyrrolo[2,3-*d*]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-(Propen-2-
 yl)amino-7-methyl-pyrrolo[2,3-*d*]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-
 (Propen-2-yl)amino-7-methyl-pyrrolo[2,3-*d*]pyrimidin-4-yl)-O-methyl-hydroxylamine,
 30 N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3-*d*]pyrimidin-4-yl)-N,O-dimethyl-
 hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3-*d*]pyrimidin-4-yl)-O-
 methyl-hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3-*d*]pyrimidin-4-yl)-
 hydrazine, N-Methyl-N-(2-*n*-propylamino-7-methyl-pyrrolo[2,3-*d*]pyrimidin-4-yl)-
 hydrazine, N,N-Dimethyl-N'-(2-*n*-propylamino-7-methyl-pyrrolo[2,3-*d*]pyrimidin-4-

yl)-hydrazine, N-(2,4-Bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine, N-(2,4,6-Tris-*n*-propylamino)-[1,3,5]triazine, N-(2,4,6-Tris-*n*-propylamino)-1,3-pyrimidine, N-(2,4-Bis-*n*-propylamino)-N-(6-*i*-propylamino)-1,3-pyrimidine, a salt thereof and mixtures thereof.

5 54. The method of claim 52, wherein the subject is a mammal.

55. The method of claim 54, wherein the mammal is human.

56. A method of inhibiting the TASK-1 (KCNK3) channel in a subject in need thereof, the method comprising administering to the subject an effective amount of a pharmaceutical formulation comprising at least one
10 pharmaceutically acceptable carrier and at least one compound of formula (I):



(I), wherein

R^1 and R^2 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl; or R^1
15 and R^2 combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

R^3 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-NR^1R^2$, $-C(O)OR^1$, acyl, or aryl;
20

R^4 is H, alkyl, or substituted alkyl;

R^5 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-OR^1$, $-NR^1R^2$, $-C(O)OR^1$, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, or substituted heterocyclic; or R^3 and R^5 combine
25 as to form a biradical selected from the group consisting of 3,6,9-trioxa-undecane-1,11-diyl and 3,6-dioxa-octane-1,8-diyl;

R^6 is H, alkyl, substituted alkyl or alkenyl;

X is a bond, O or NR⁴; and,

Y is N, CR⁶ or C; wherein:

if Y is N or CR⁶, then bond b¹ is nil and:

(i) Z is H, bond b² is a single bond, and A is CH; or,

5 (ii) Z is nil, bond b² is nil, and A is a single bond;

and,

if Y is C, then bond b¹ is a single bond, and:

(i) Z is CH₂, bond b² is a single bond, and A is CH; or,

(ii) Z is CH, bond b² is a double bond, and A is C;

10 or a salt thereof.

57. The method of claim 56, wherein the compound of formula (I) is selected from the group consisting of: N-(4,6-Bis-methylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-ethylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-Cyclopropylmethyl)-N-(6-*n*-propylamino) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-Ethylamino)-N-(6-*n*-propylamino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2-methylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2,2-dimethylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2,2-dimethylpropylamino))[1,3,5]triazin-2-yl)-N,O-dimethyl-
20 hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-(Methoxy(methyl)amino)-6-(*n*-propylamino)-1,3,5-triazin-2-yl)propionamide, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-methyl-hydroxylamine, O-Allyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine, 6-
25 (Methoxy(methyl)amino)-N²-propyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine, O-Benzyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-isopropyl-hydroxylamine, 6-[1,2]Oxazinan-2-yl-N,N'-dipropyl-[1,3,5]triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-N-methyl-hydroxylamine, O-Benzyl-N-(4,6-bis-*n*-propylamino-
30 [1,3,5]triazin-2-yl)-N-ethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-hydroxylamine, 6-((Benzyloxy)(isopropyl) amino)-N²,N⁴-dipropyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-O-

- isopropyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isobutyl-N-methyl-hydroxylamine, 6-(Methyl(thiophen-2-ylmethoxy)amino)-N²,N⁴-dipropyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-cyclopropylmethyl-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-
- 5 [1,3,5]triazin-2-yl)-O-ethyl-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-(2,2-difluoro-ethyl)-hydroxylamine, 4-N-(2-Dimethylaminoethyl)amino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4-N-(3-(1-N-Methylimidazol-2-yl)-propyl)-amino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4-N-(1-N-
- 10 Methylimidazol-2-yl)-methylamino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-(N-(2-dimethylaminoethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-(N-(pyridin-4-yl-methyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-[N-(3-methoxy-*n*-propyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-[N-
- 15 (tetrahydropyran-4-yl-methyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(5,8,11-Trioxa-2,14,16,18,19-pentaazabicyclo[13.3.1]nonadeca-1(18),15(19),16(17)-trien-17-yl)-N,O-dimethylhydroxylamine, 2,6-Bis-(N-*n*-propylamino)-[1,3]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N',N'-dimethylhydrazine, N-(4,6-Bis-*n*-
- 20 propylamino-[1,3,5]triazin-2-yl)-N-methyl-N'-methylhydrazine, 2-(*n*-Propyl)amino-4-(*i*-propylamino-7-methyl-pyrrolidino[2,3-*d*]pyrimidine, 2-(*n*-Propyl)amino-4-dimethylamino-7-methyl-pyrrolidino[2,3-*d*]pyrimidine, 2-(*n*-Propyl)amino-4-methylamino-7-methyl-pyrrolidino[2,3-*d*]pyrimidine, 2-(*n*-Propyl)amino-4-(*i*-propyl)amino-7-*i*-propyl-pyrrolidino[2,3-*d*]pyrimidine, 2,4-Bis-(*n*-propyl)amino-7H-
- 25 pyrrolidino[2,3-*d*]pyrimidine, 2-(*n*-Propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-methyl-pyrrolidino[2,3-*d*]pyrimidine, 8-(7-Methyl-2-(*n*-propylamino)-pyrrolidino[2,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol, N-(2-Propylamino-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3-*d*]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-
- 30 (Propen-2-yl)amino-7-methyl-pyrrolo[2,3-*d*]pyrimidin-4-yl)-O-methyl-hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3-*d*]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3-*d*]pyrimidin-4-yl)-O-methyl-hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3-*d*]pyrimidin-4-yl)-hydrazine, N-Methyl-N-(2-*n*-propylamino-7-methyl-pyrrolo[2,3-*d*]pyrimidin-4-yl)-

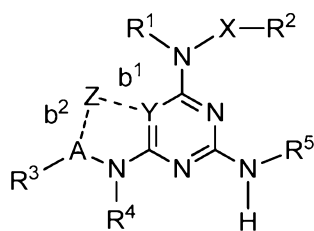
hydrazine, N,N-Dimethyl-N'-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine, N-(2,4-Bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine, N-(2,4,6-Tris-*n*-propylamino)-[1,3,5]triazine, N-(2,4,6-Tris-*n*-propylamino)-1,3-pyrimidine, N-(2,4-Bis-*n*-propylamino)-N-(6-*i*-propylamino)-1,3-pyrimidine, a salt thereof and mixtures thereof.

58. The method of claim 57, wherein the compound of formula (I) is selected from the group consisting of: N-(4,6-Bis-*n*-propylamino-1,3,5]triazin-2-yl)-O-methyl-hydroxylamine; N-(4,6-Bis-*n*-propylamino-1,3,5]triazin-2-yl)-N',N'-dimethylhydrazine; N-(2,4-Bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine; N-[(2,6-Bis-*n*-propylamino)-pyrimidin-4-yl]-N,O-dimethyl-hydroxylamine; N,N-Dimethyl-N'-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine; a salt thereof and mixtures thereof.

59. The method of claim 56, wherein the subject is a mammal.

60. The method of claim 59, wherein the mammal is human.

61. A method of increasing minute ventilation in a subject in need thereof, the method comprising administering to the subject an effective amount of a pharmaceutical formulation comprising at least one pharmaceutically acceptable carrier and at least one compound of formula (I):



(I), wherein

R¹ and R² are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl; or R¹ and R² combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

R^3 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-NR^1R^2$, $-C(O)OR^1$, acyl, or aryl;

R^4 is H, alkyl, or substituted alkyl;

R^5 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, $-OR^1$, $-NR^1R^2$, $-C(O)OR^1$, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, or substituted heterocyclic; or R^3 and R^5 combine as to form a biradical selected from the group consisting of 3,6,9-trioxa-undecane-1,11-diyl and 3,6-dioxa-octane-1,8-diyl;

R^6 is H, alkyl, substituted alkyl or alkenyl;

10 X is a bond, O or NR^4 ; and,

Y is N, CR^6 or C; wherein:

if Y is N or CR^6 , then bond b^1 is nil and:

(i) Z is H, bond b^2 is a single bond, and A is CH; or,

(ii) Z is nil, bond b^2 is nil, and A is a single bond;

15 and,

if Y is C, then bond b^1 is a single bond, and:

(i) Z is CH_2 , bond b^2 is a single bond, and A is CH; or,

(ii) Z is CH, bond b^2 is a double bond, and A is C;

or a salt thereof.

20 62. The method of claim 61, wherein the compound of formula (I) is selected from the group consisting of: N-(4,6-Bis-methylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-ethylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-Cyclopropylmethyl)-N-(6-*n*-propylamino) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-Ethylamino)-N-(6-*n*-propylamino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2-methylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2,2-dimethylpropylamino)) [1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(Bis-4,6-(2,2-dimethylpropylamino))[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, N-(4-(Methoxy(methyl)amino)-6-(*n*-propylamino)-1,3,5-triazin-2-yl)propionamide, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-methyl-hydroxylamine, O-Allyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-hydroxylamine, 6-

(Methoxy(methyl)amino)-N²-propyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine, O-Benzyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-isopropyl-hydroxylamine, 6-[1,2]Oxazinan-2-yl-

5 N,N'-dipropyl-[1,3,5]triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-N-methyl-hydroxylamine, O-Benzyl-N-(4,6-bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isopropyl-hydroxylamine, 6-((Benzyloxy)(isopropyl) amino)-N²,N⁴-dipropyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-ethyl-O-

10 isopropyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-isobutyl-N-methyl-hydroxylamine, 6-(Methyl(thiophen-2-ylmethoxy)amino)-N²,N⁴-dipropyl-1,3,5-triazine-2,4-diamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-cyclopropylmethyl-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-O-ethyl-N-methyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-

15 [1,3,5]triazin-2-yl)-O-(2,2-difluoro-ethyl)-hydroxylamine, 4-N-(2-Dimethylaminoethyl)amino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4-N-(3-(1-N-Methylimidazol-2-yl)-propyl)-amino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4-N-(1-N-Methylimidazol-2-yl)-methylamino-6-N-(*n*-propyl)amino-[1,3,5]triazin-2-yl)-N,O-

20 dimethyl-hydroxylamine, 4,6-Bis-(N-(2-dimethylaminoethyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-(N-(pyridin-4-yl-methyl)amino)-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-[N-(3-methoxy-*n*-propyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, 4,6-Bis-[N-(tetrahydropyran-4-yl-methyl)amino]-[1,3,5]triazin-2-yl)-N,O-dimethyl-

25 hydroxylamine, N-(5,8,11-Trioxa-2,14,16,18,19-pentaazabicyclo[13.3.1]nonadeca-1(18),15(19),16(17)-trien-17-yl)-N,O-dimethylhydroxylamine, 2,6-Bis-(N-*n*-propylamino)-[1,3]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N',N'-dimethylhydrazine, N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N-methyl-N'-methylhydrazine, 2-(*n*-Propyl)amino-

30 4-(*i*-propylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine, 2-(*n*-Propyl)amino-4-dimethylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine, 2-(*n*-Propyl)amino-4-methylamino-7-methyl-pyrrolidino[2,3-d]pyrimidine, 2-(*n*-Propyl)amino-4-(*i*-propyl)amino-7-*i*-propyl-pyrrolidino[2,3-d]pyrimidine, 2,4-Bis-(*n*-propyl)amino-7H-pyrrolidino[2,3-d]pyrimidine, 2-(*n*-Propyl)amino-4-(4-hydroxypiperidin-1-yl)-7-

methyl-pyrrolidino[2,3-d]pyrimidine, 8-(7-Methyl-2-(*n*-propylamino)-pyrrolidino[2,3-d]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol, N-(2-Propylamino-7H-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-(Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-
 5 (Propen-2-yl)amino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-N,O-dimethyl-hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-O-methyl-hydroxylamine, N-(2-*n*-Propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine, N-Methyl-N-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-
 10 hydrazine, N,N-Dimethyl-N'-(2-*n*-propylamino-7-methyl-pyrrolo[2,3d]pyrimidin-4-yl)-hydrazine, N-(2,4-Bis-*n*-propylamino)-N-(6-methylamino)-[1,3,5]triazine, N-(2,4,6-Tris-*n*-propylamino)-[1,3,5]triazine, N-(2,4,6-Tris-*n*-propylamino)-1,3-pyrimidine, N-(2,4-Bis-*n*-propylamino)-N-(6-*i*-propylamino)-1,3-pyrimidine, a salt thereof and mixtures thereof.

15 63. The method of claim 62, wherein the compound of formula (I) is N-(4,6-Bis-*n*-propylamino-[1,3,5]triazin-2-yl)-N,O-dimethyl-hydroxylamine, or a salt thereof.

 64. The method of claim 61, wherein the pharmaceutical formulation is administered via intravenous infusion.

20 65. The method of claim 64, wherein the infusion dose of the pharmaceutical formulation is at least about 0.016 mg/kg/min.

 66. The method of claim 65, wherein the infusion dose of the pharmaceutical formulation is about 0.016 mg/kg/min.

25 67. The method of claim 61, wherein the infusion dose of the pharmaceutical composition produce plasma concentrations of at least about 726 ng/mL in the subject.

 68. The method of claim 61, wherein the subject is a mammal.

 69. The method of claim 68, wherein the mammal is human.

Fig.1

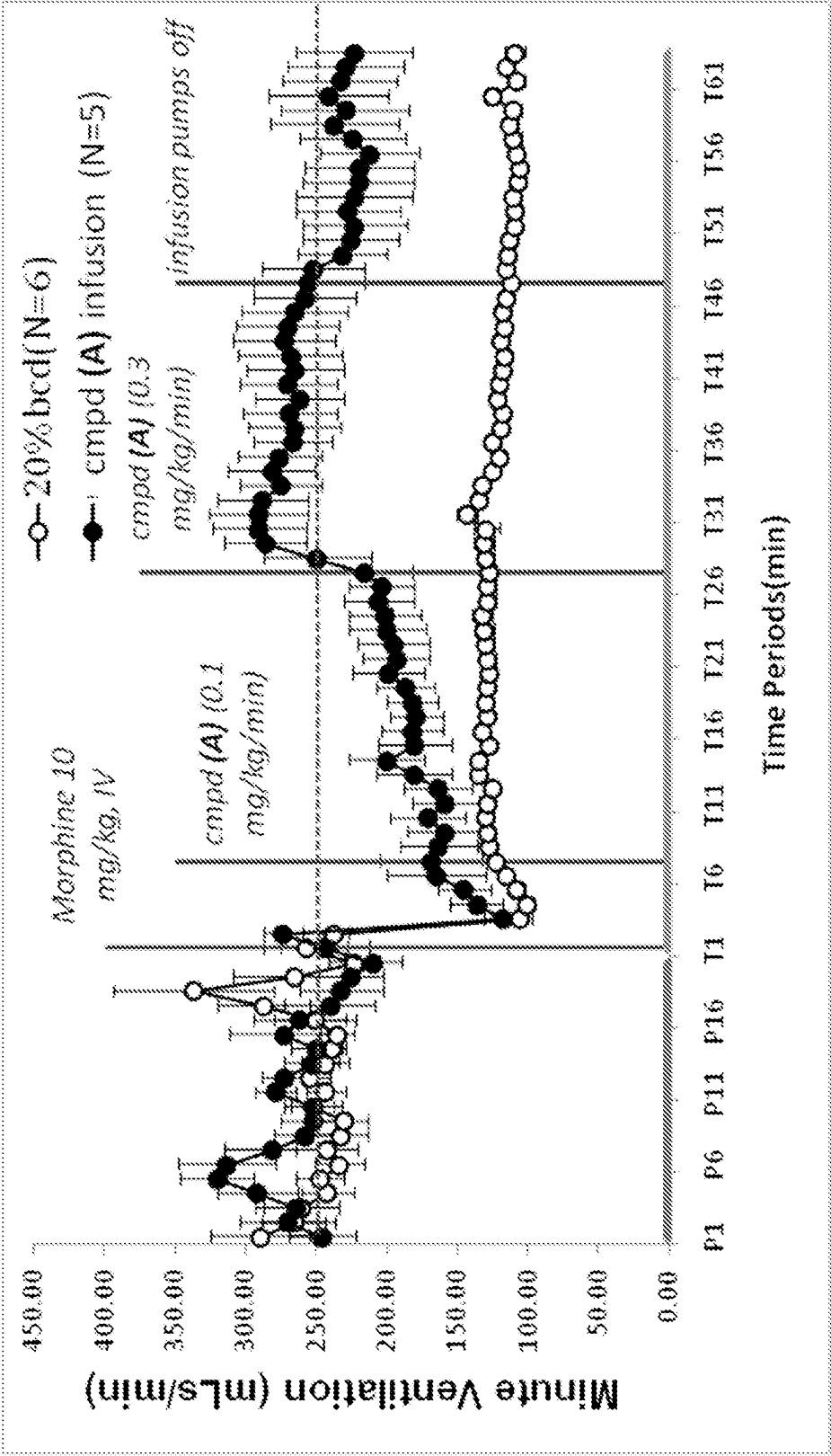


Fig. 2A

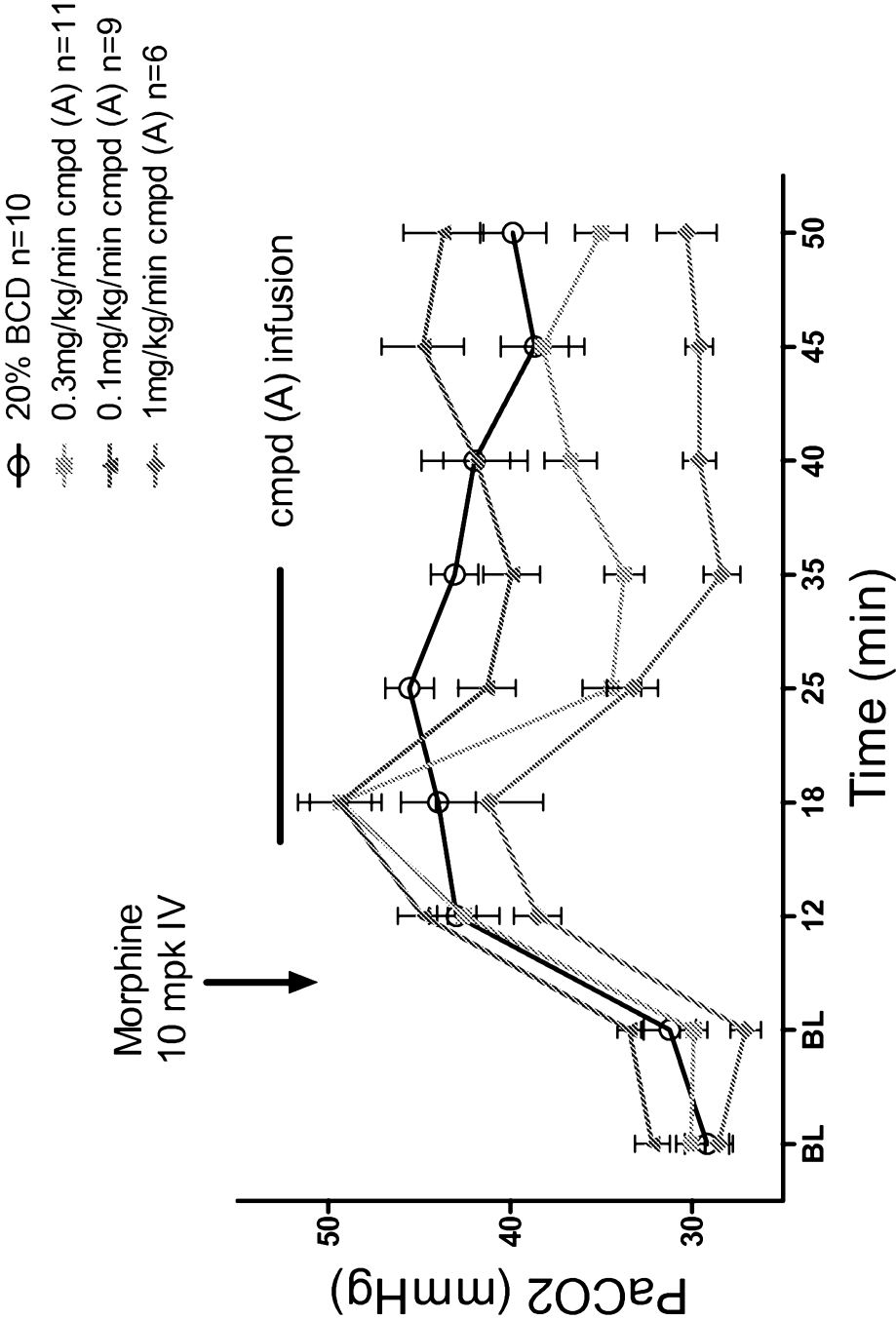


Fig. 2B

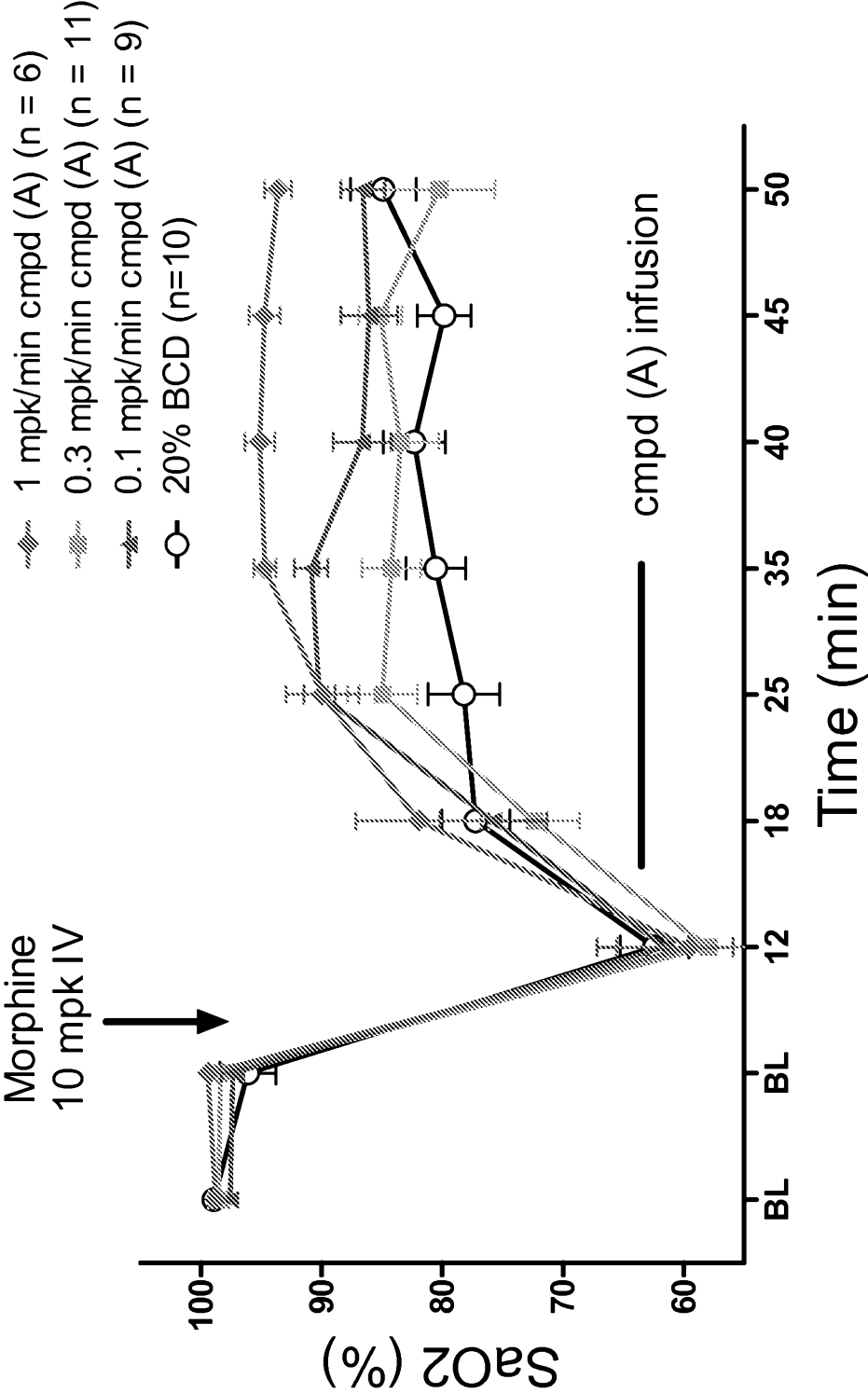


Fig. 3

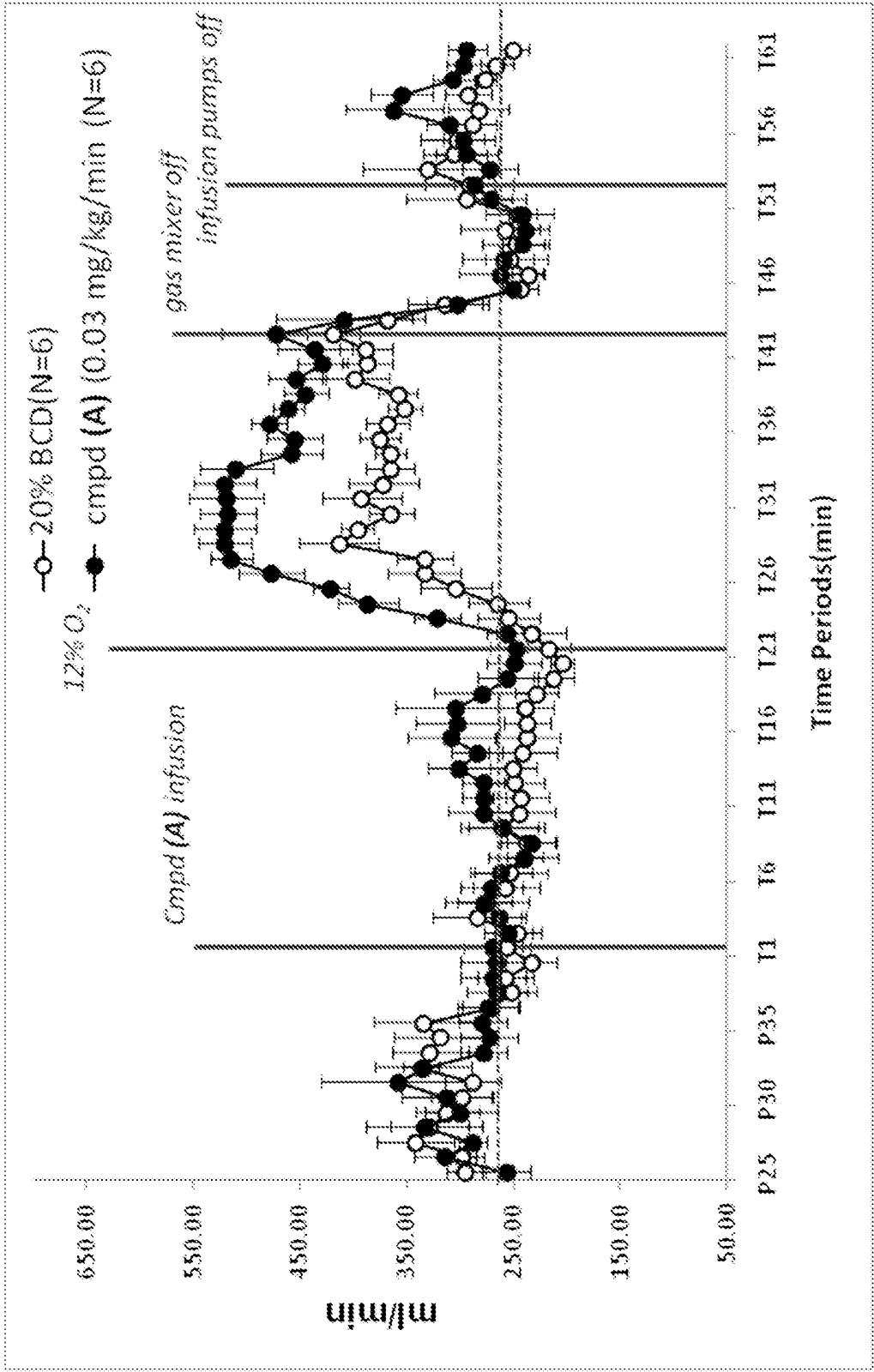
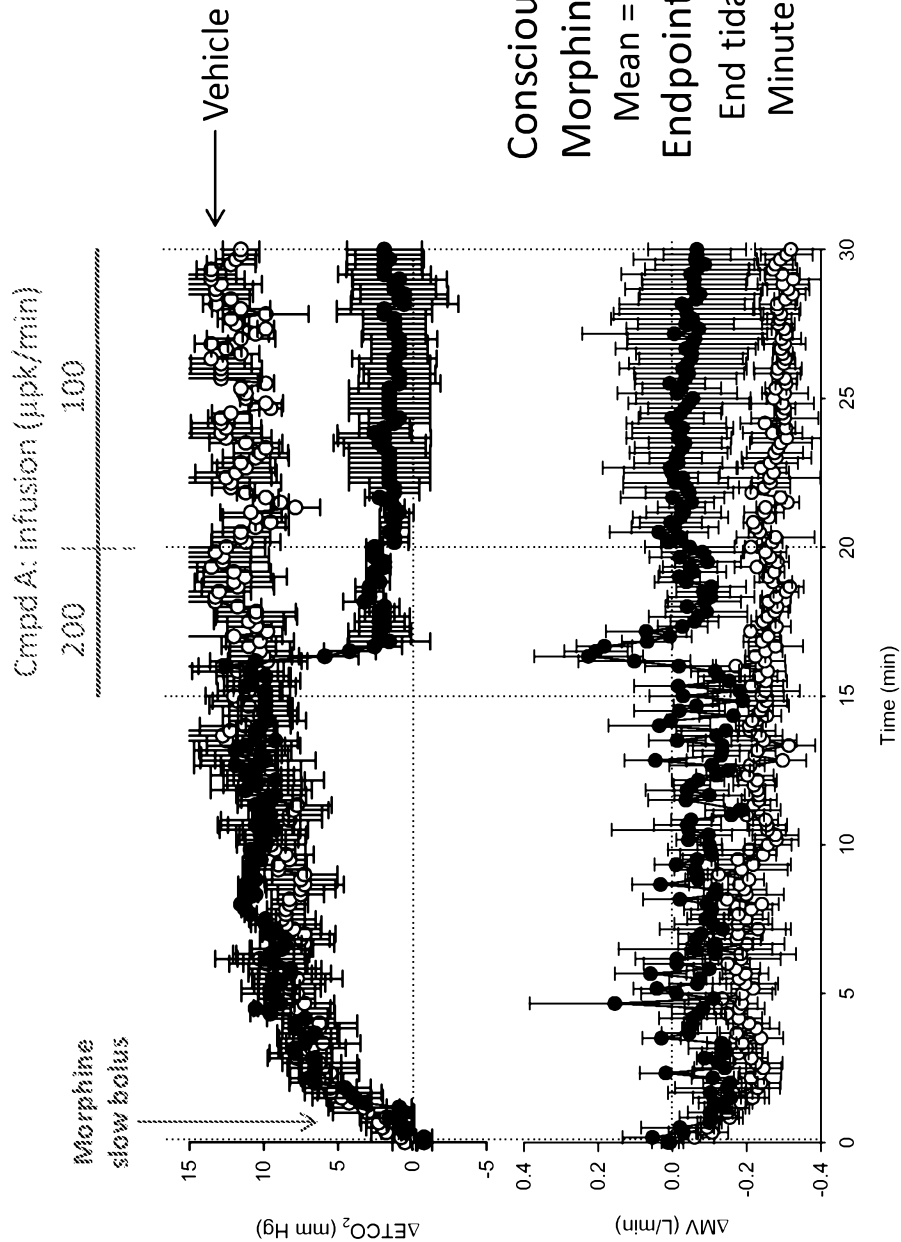


Fig. 4



Conscious animals: n = 3
Morphine: 2 min bolus
Mean = 3.4 0.5 mg/kg IV
Endpoints:
End tidal CO_2 (ETCO_2)
Minute ventilation

Fig. 5

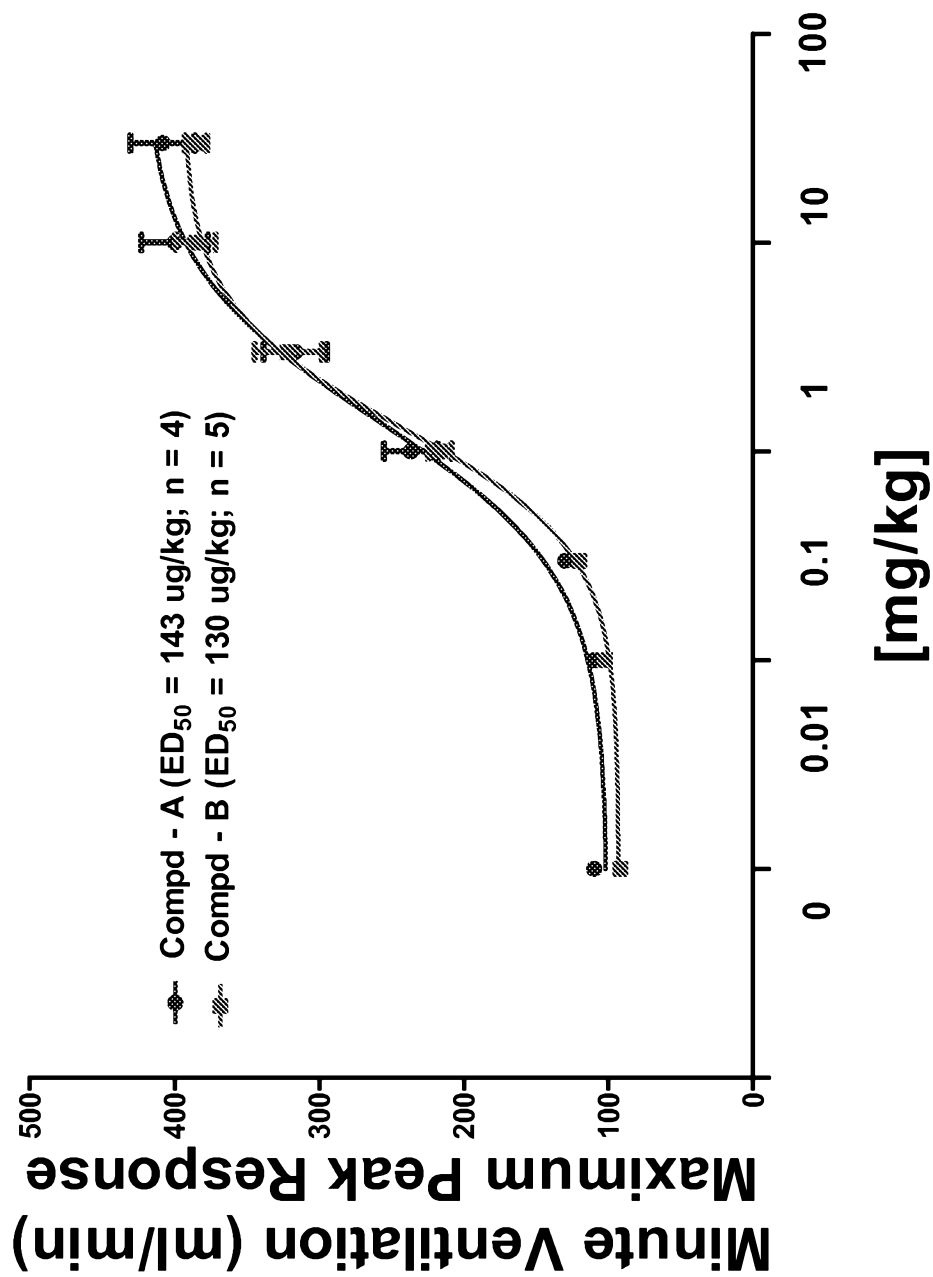


Fig. 6

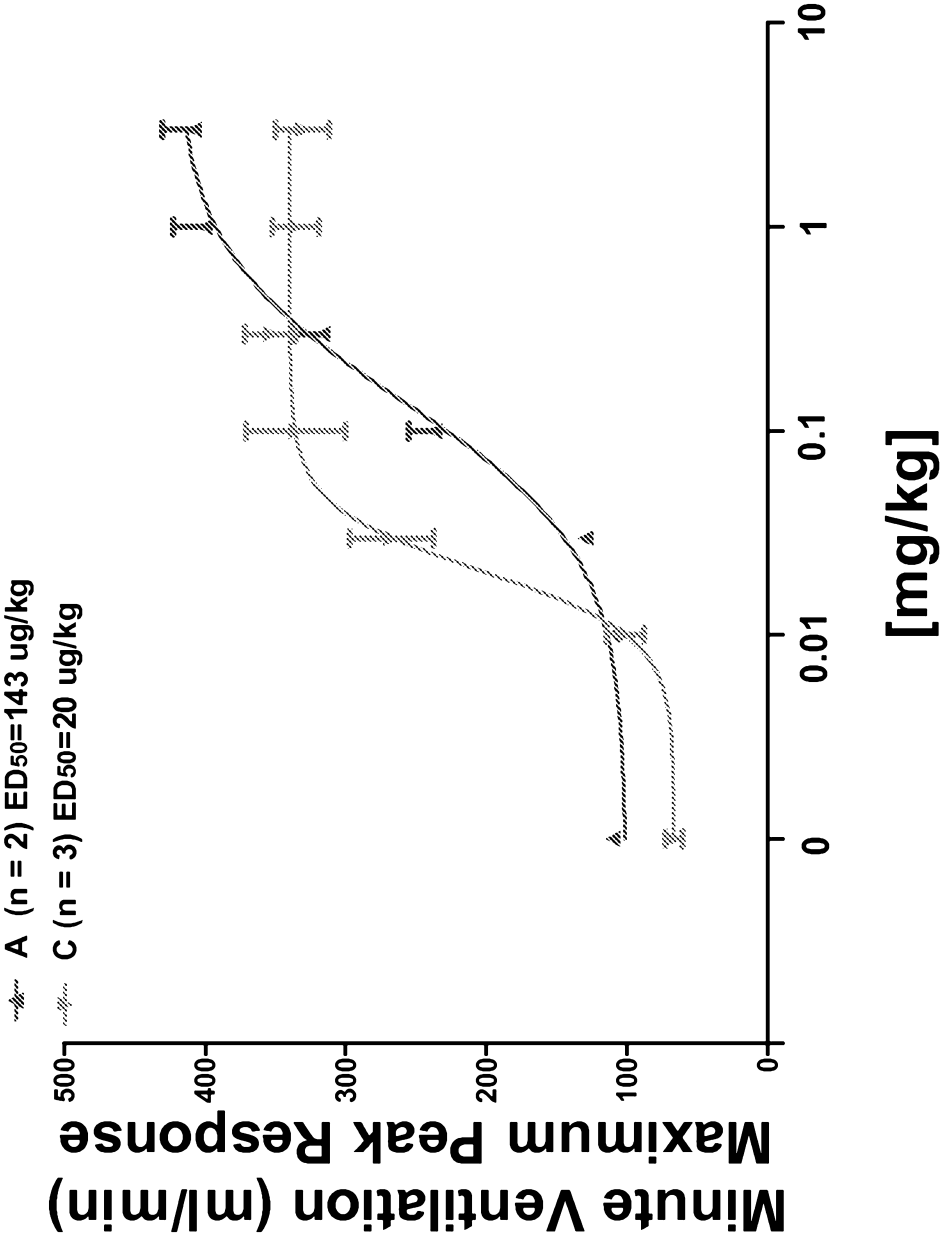


Fig. 7A

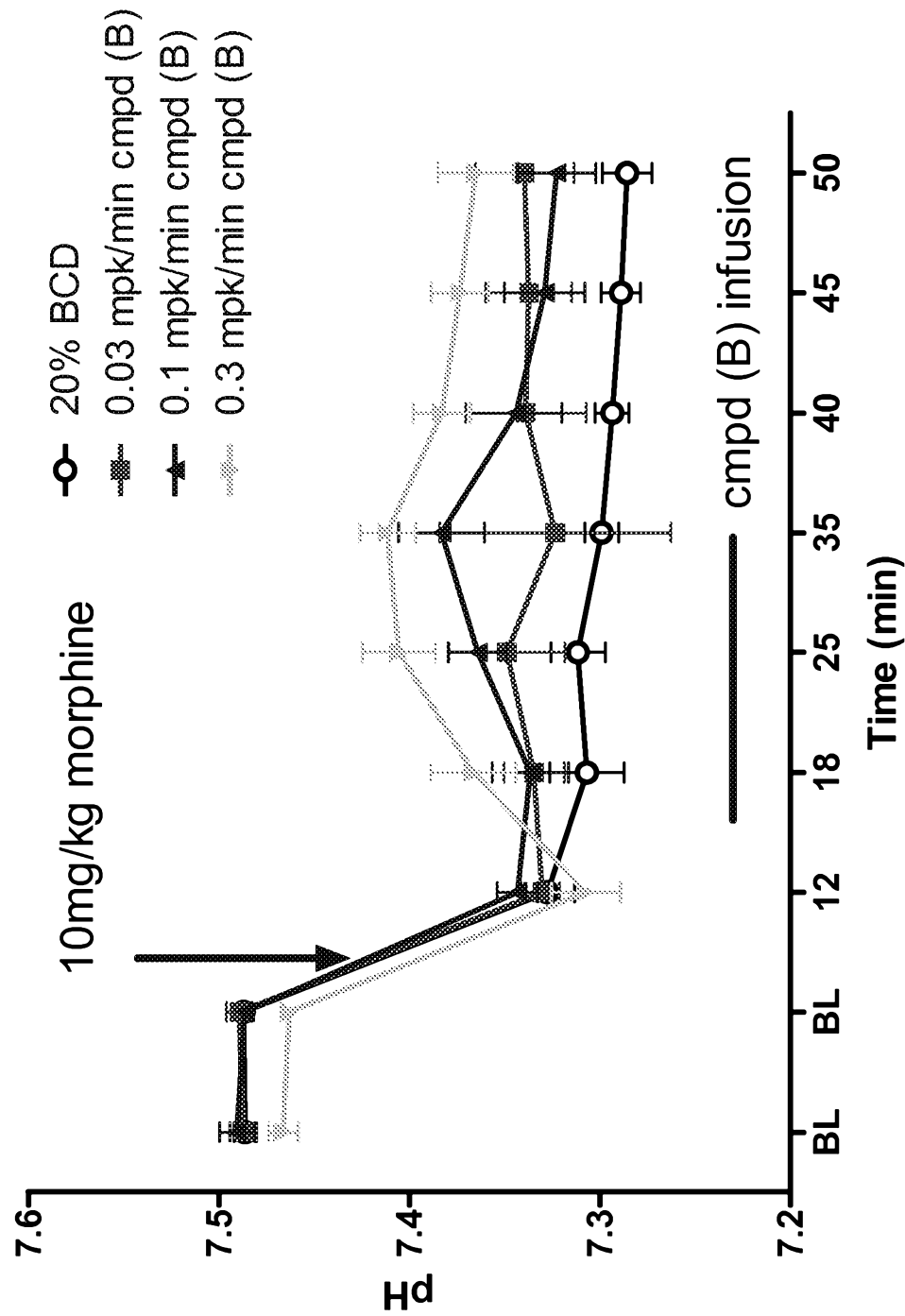


Fig. 7B

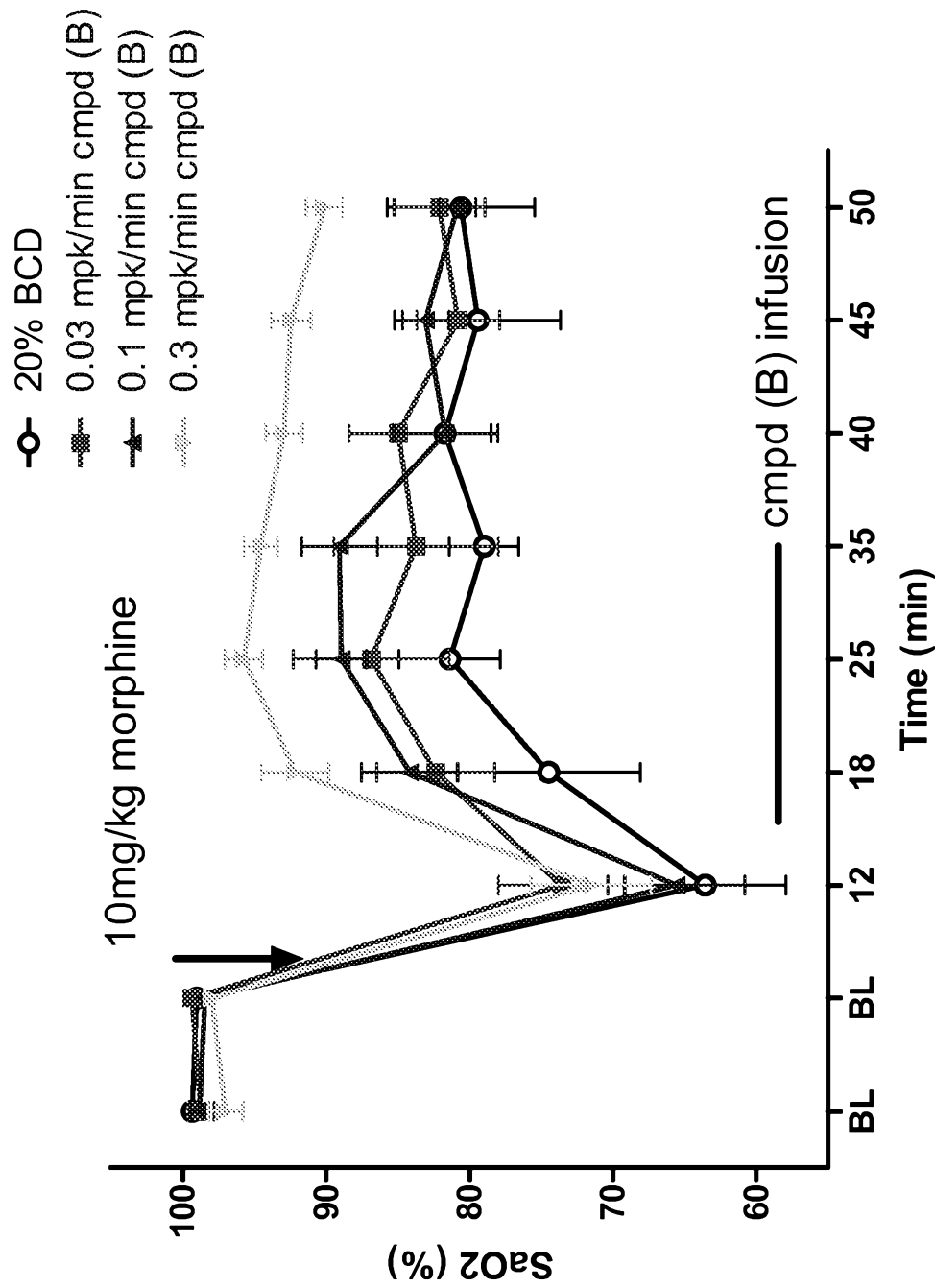


Fig. 7C

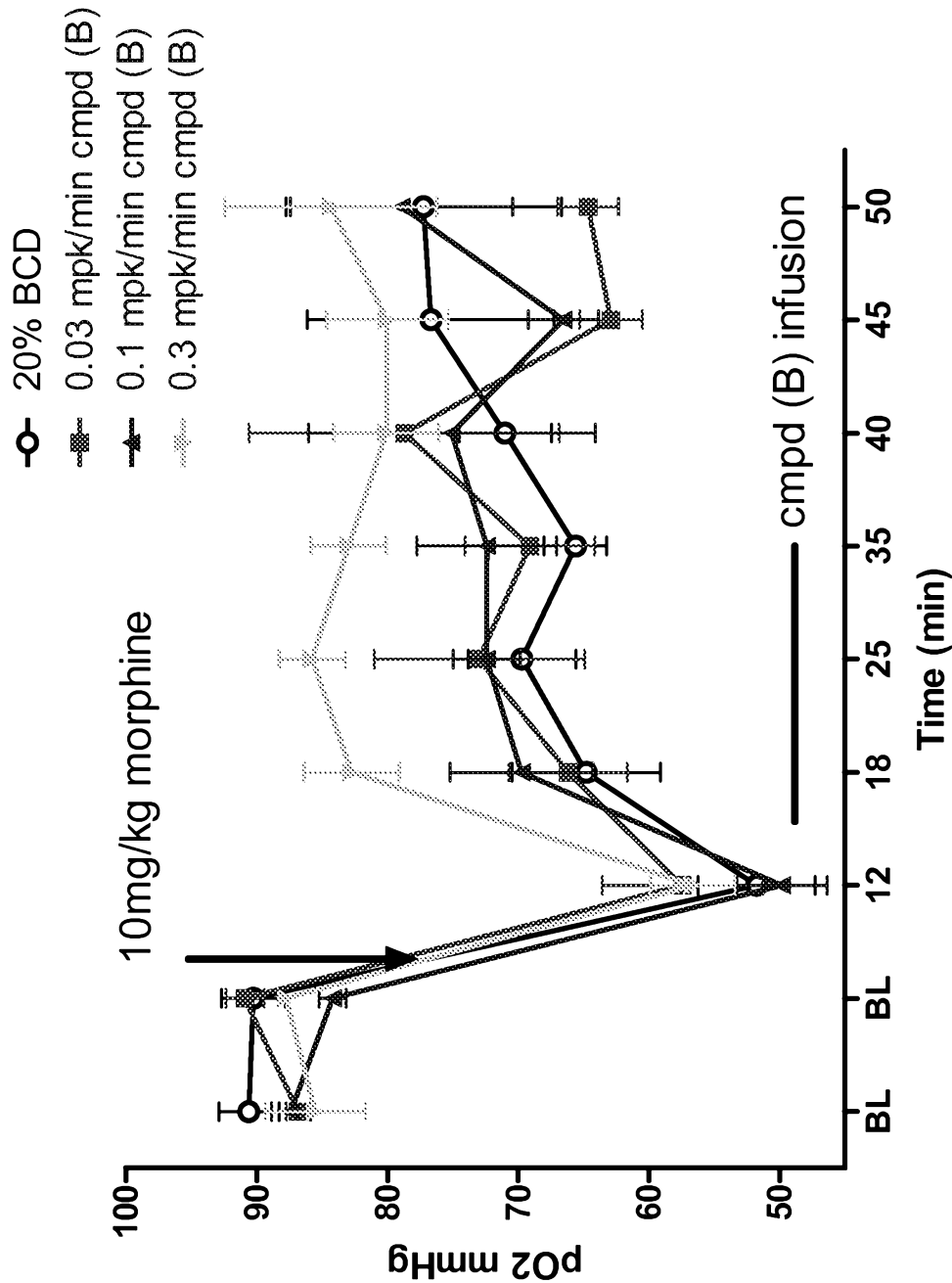


Fig. 7D

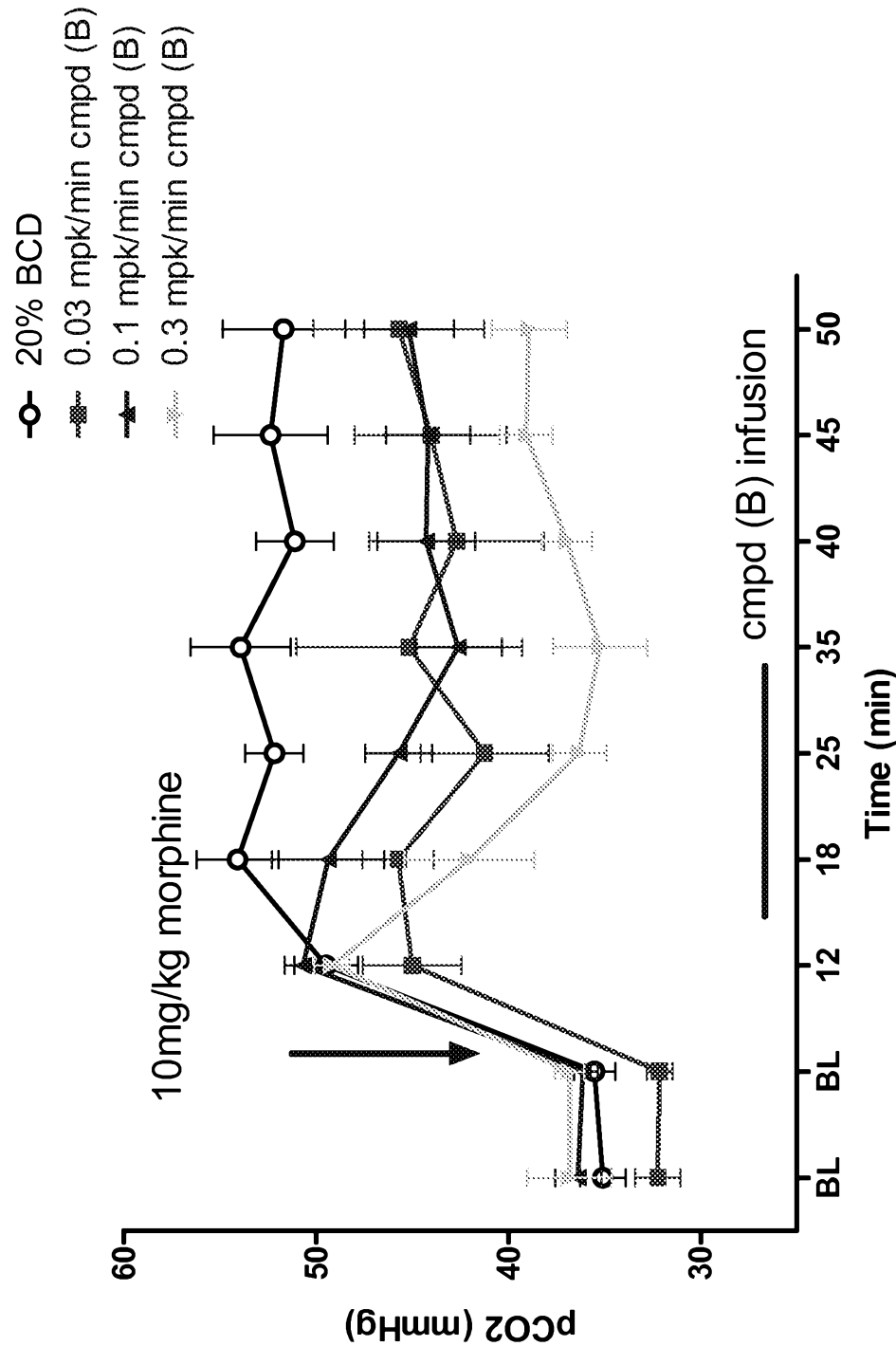


Fig. 8A

pO₂

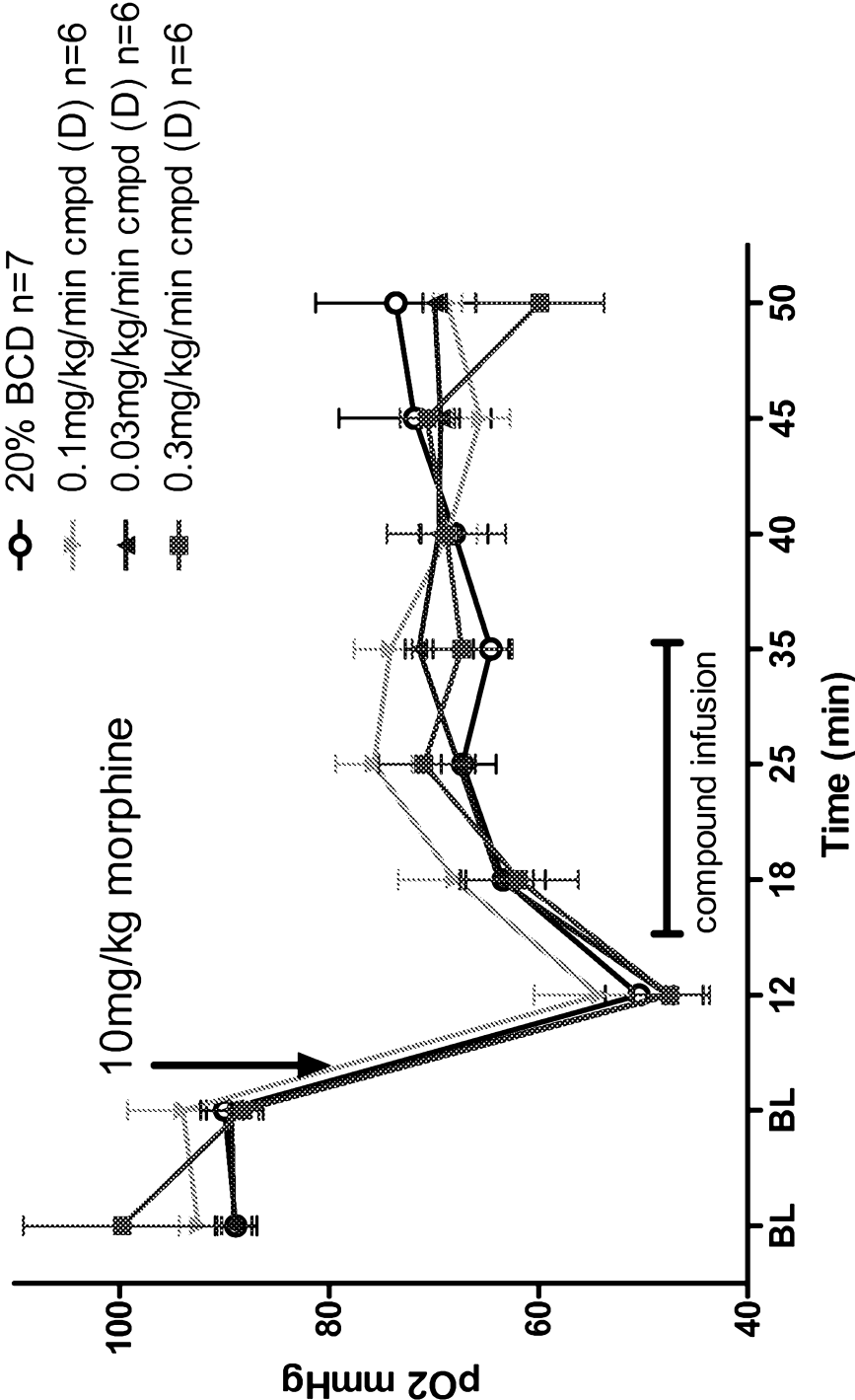


Fig. 8B

SaO2

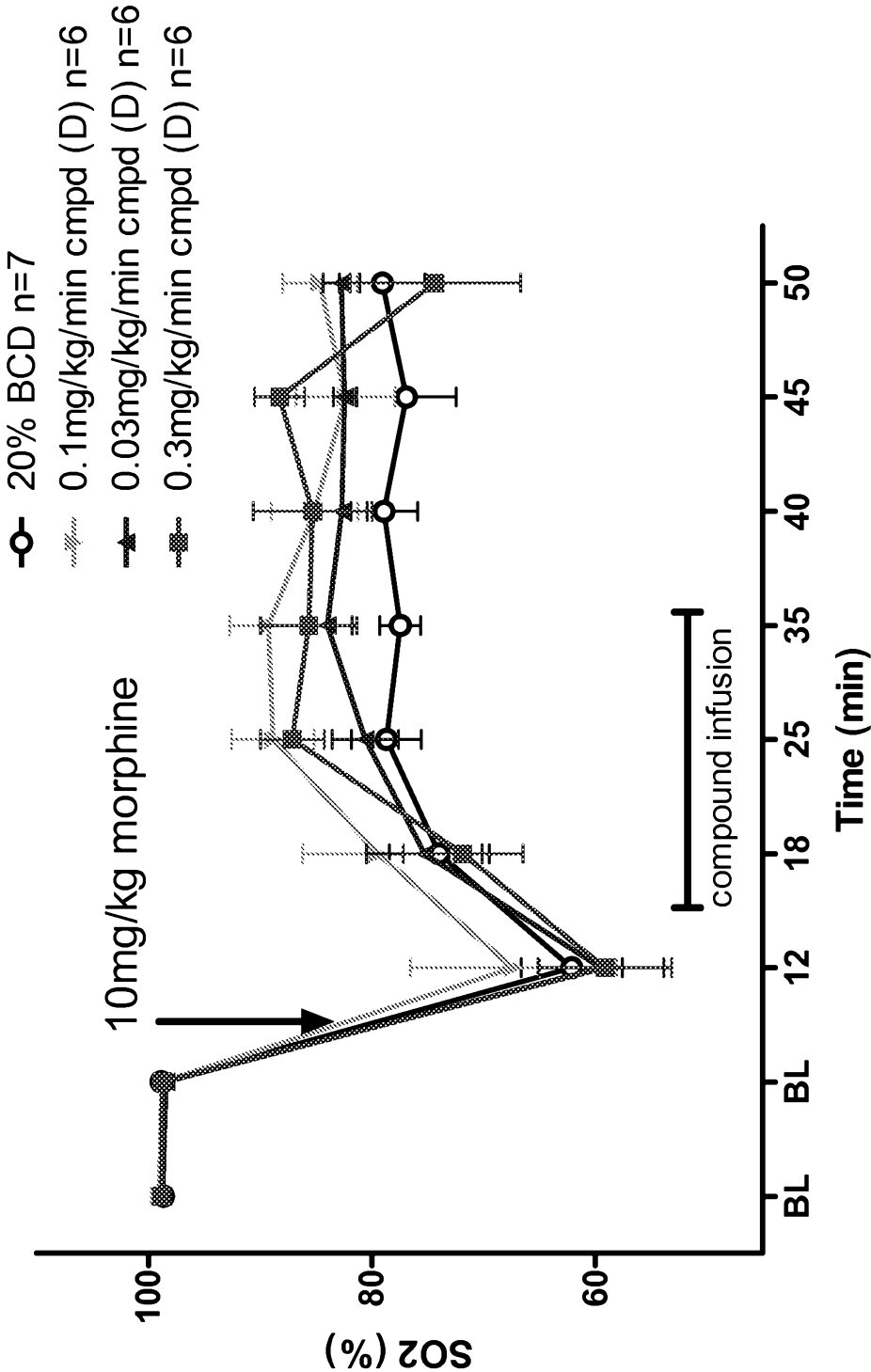


Fig. 8C

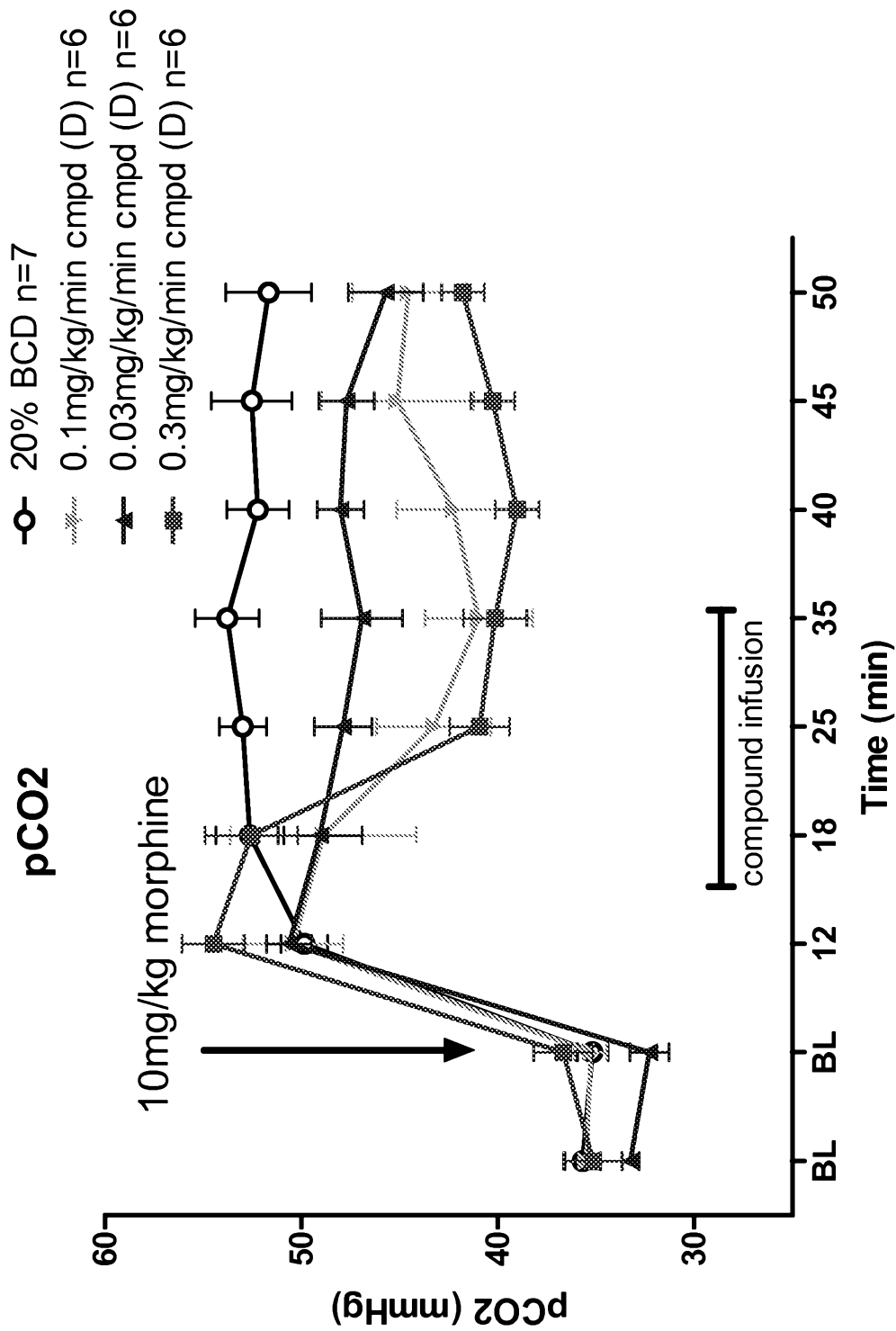


Fig. 8D

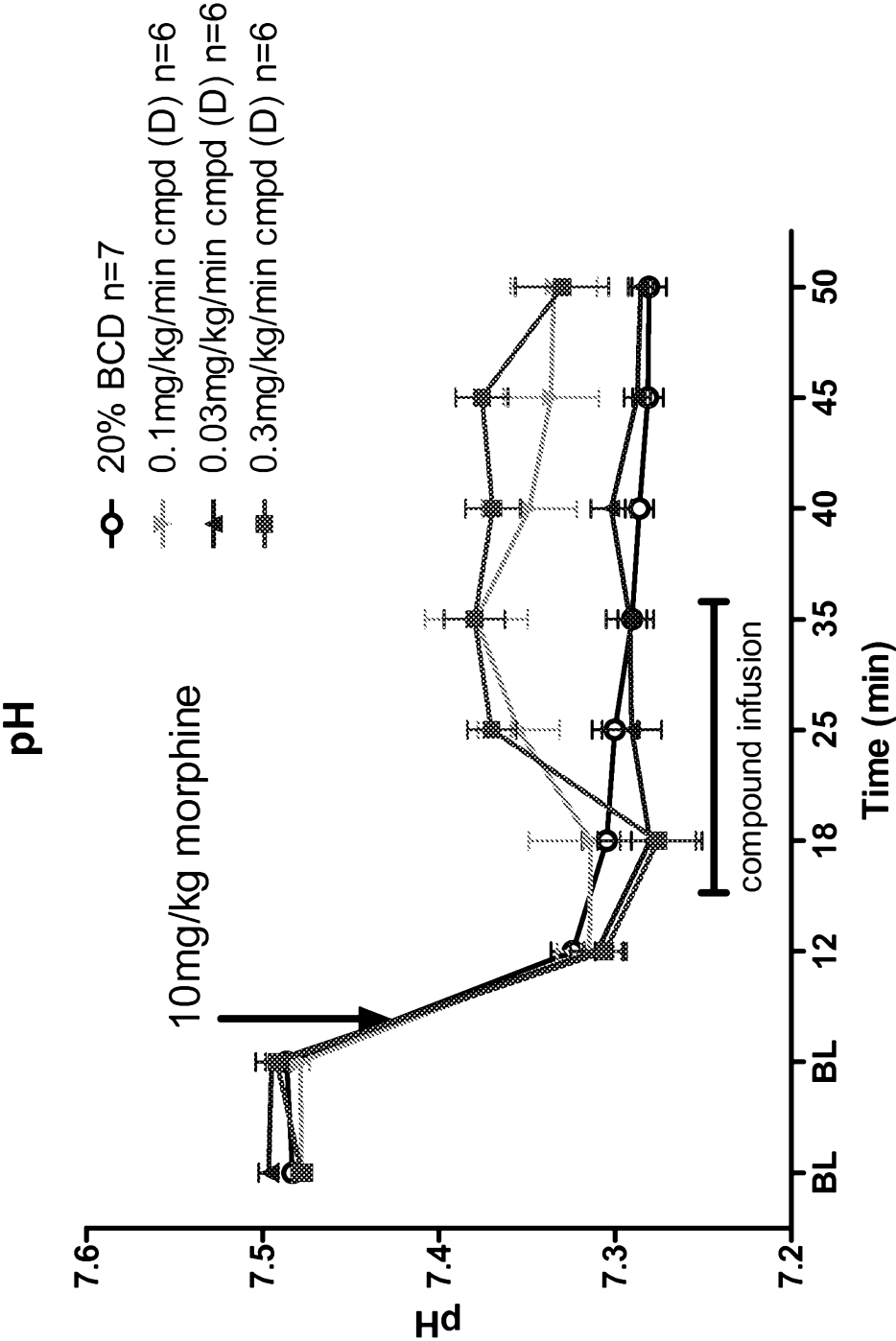


Fig. 9

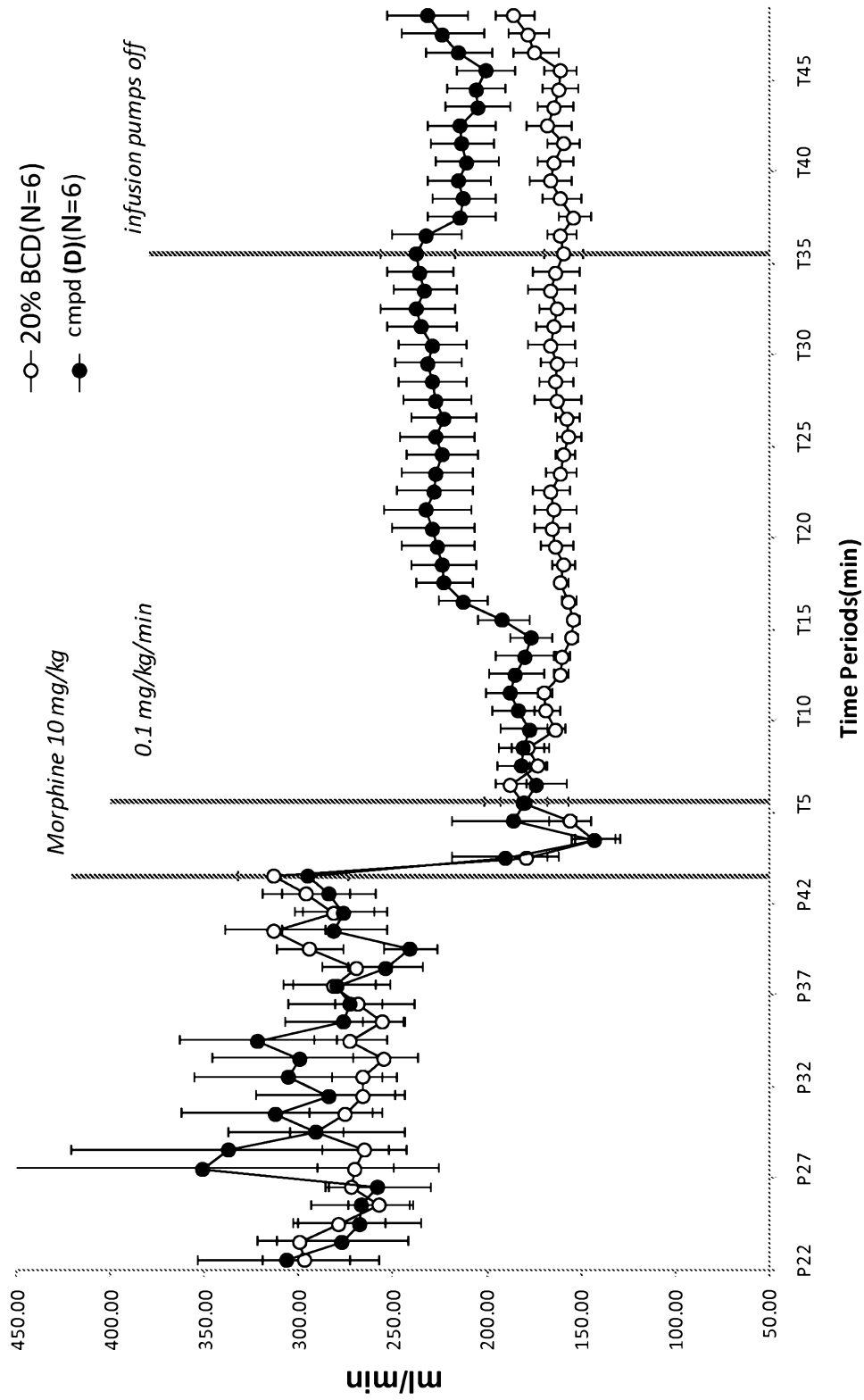


Fig. 10

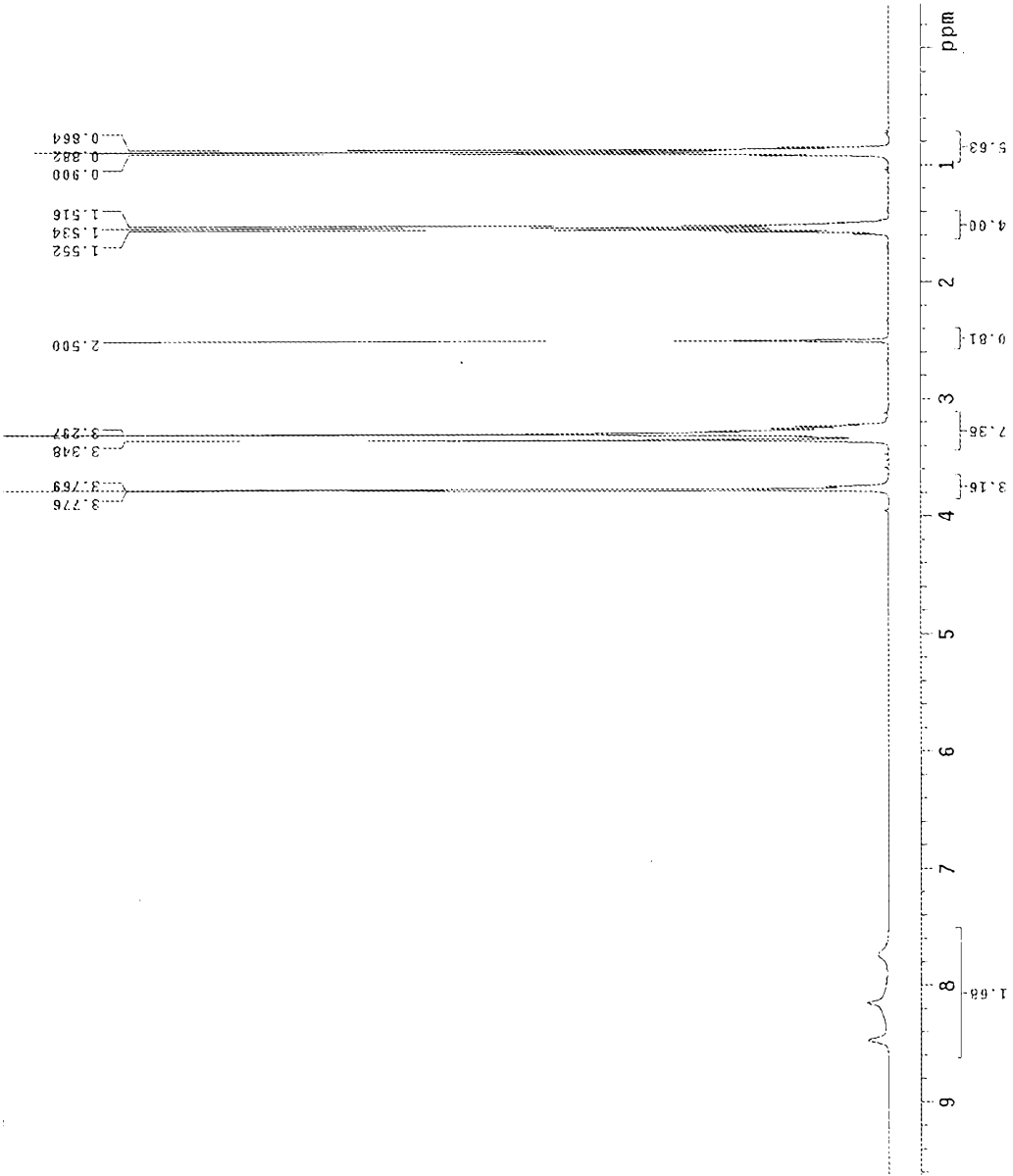


Fig. 11

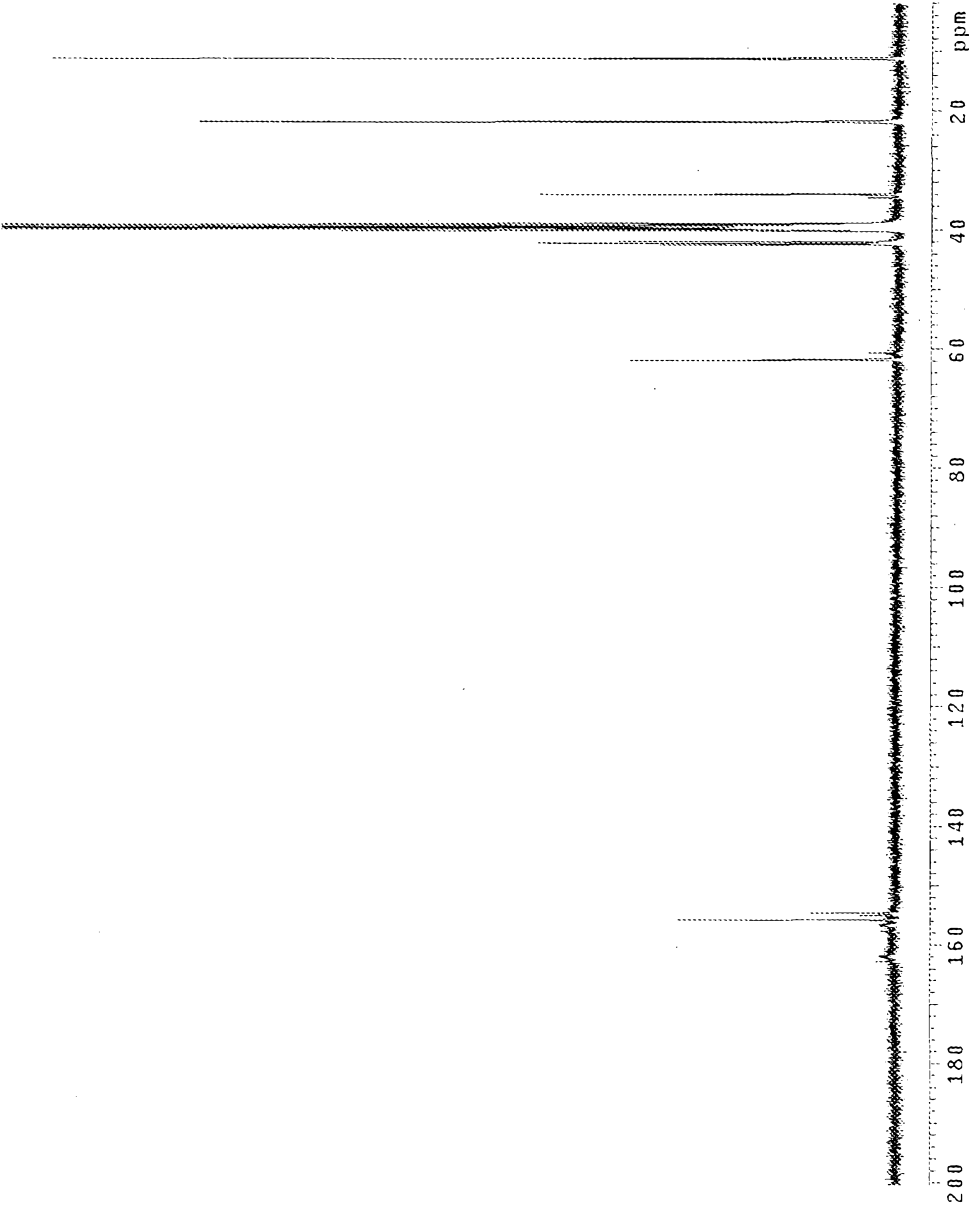


Fig. 12

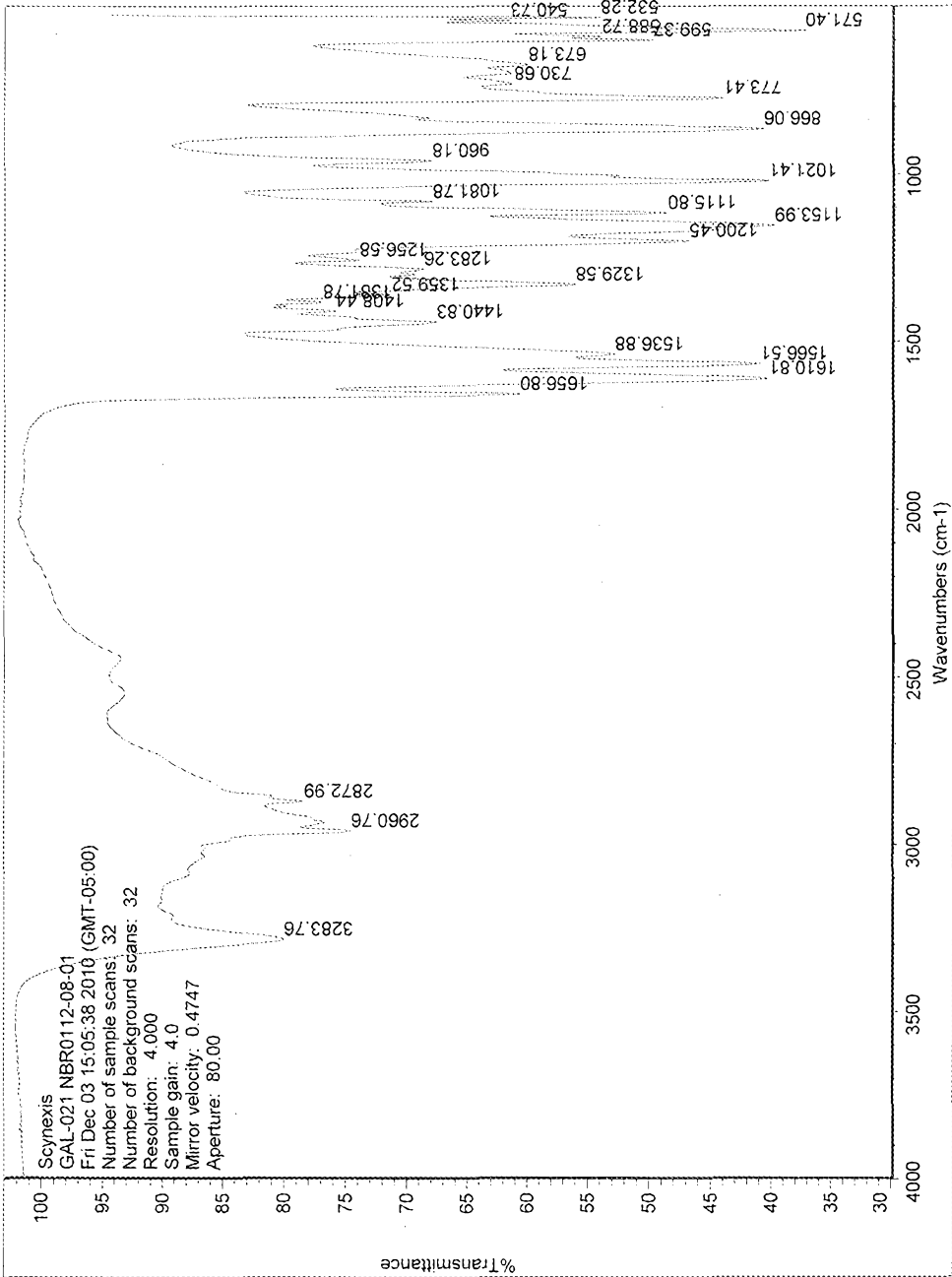


Fig. 13

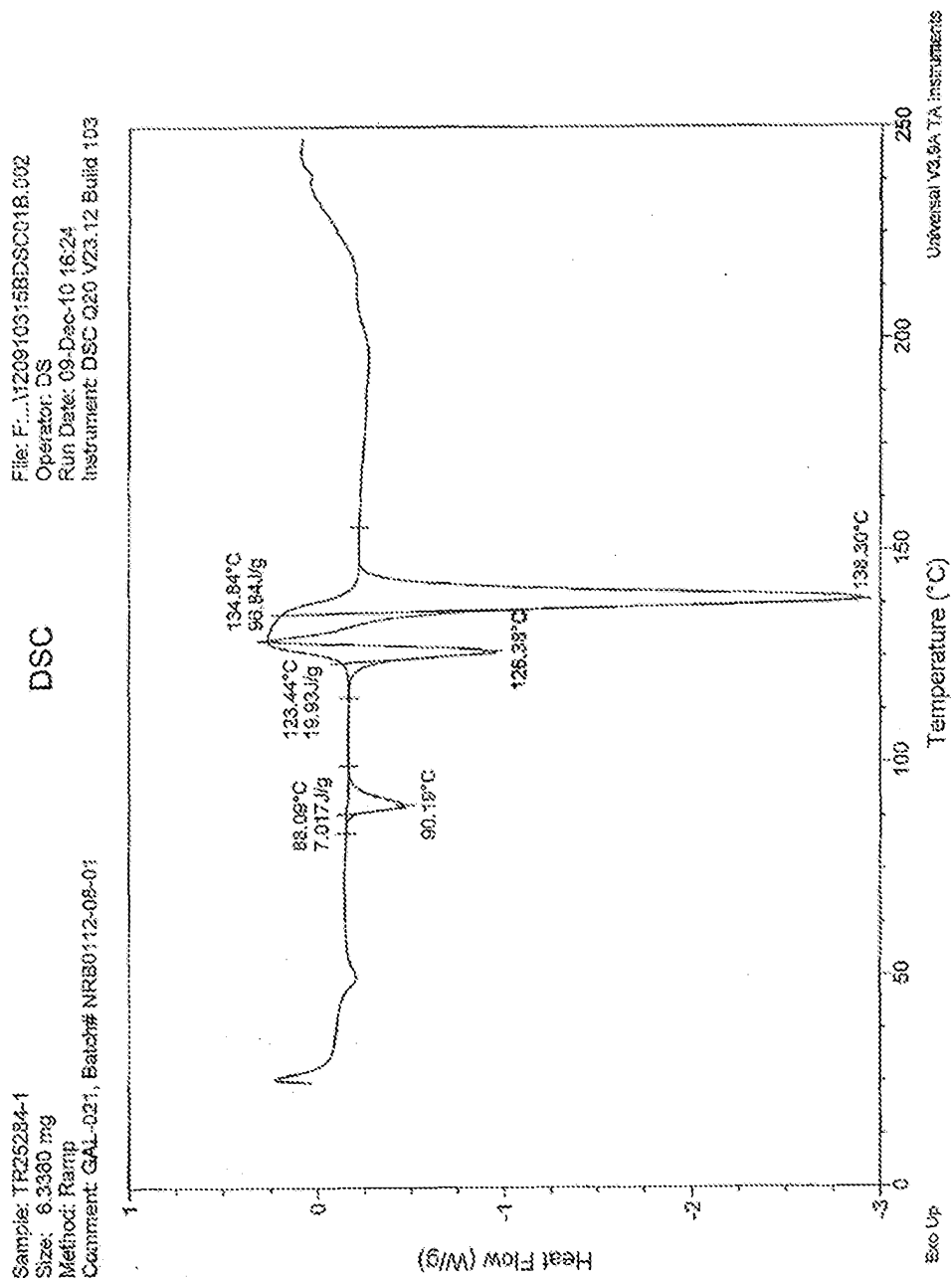


Fig. 14

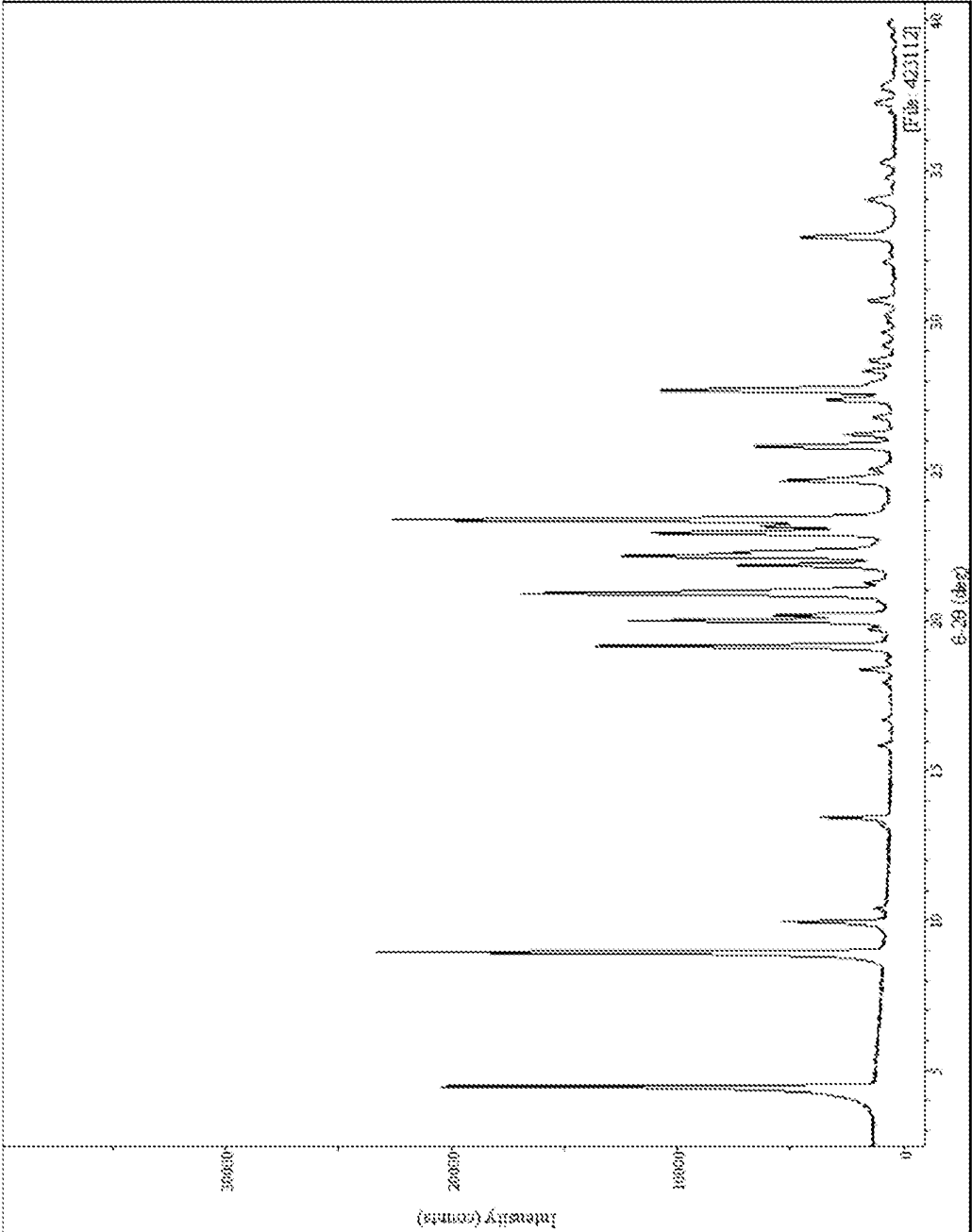


Fig. 15

Parameter: MV

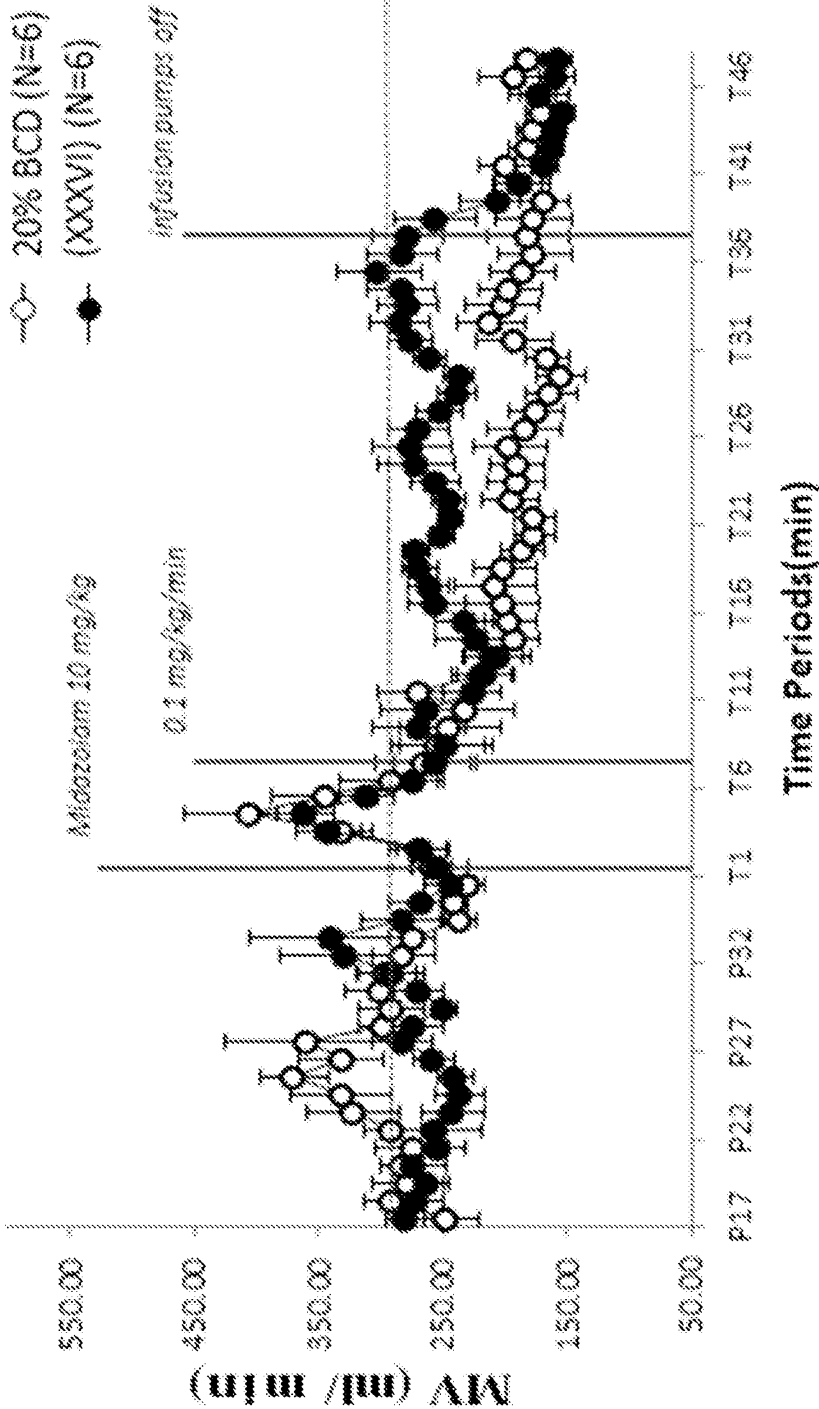


Fig. 16
Parameter: TV

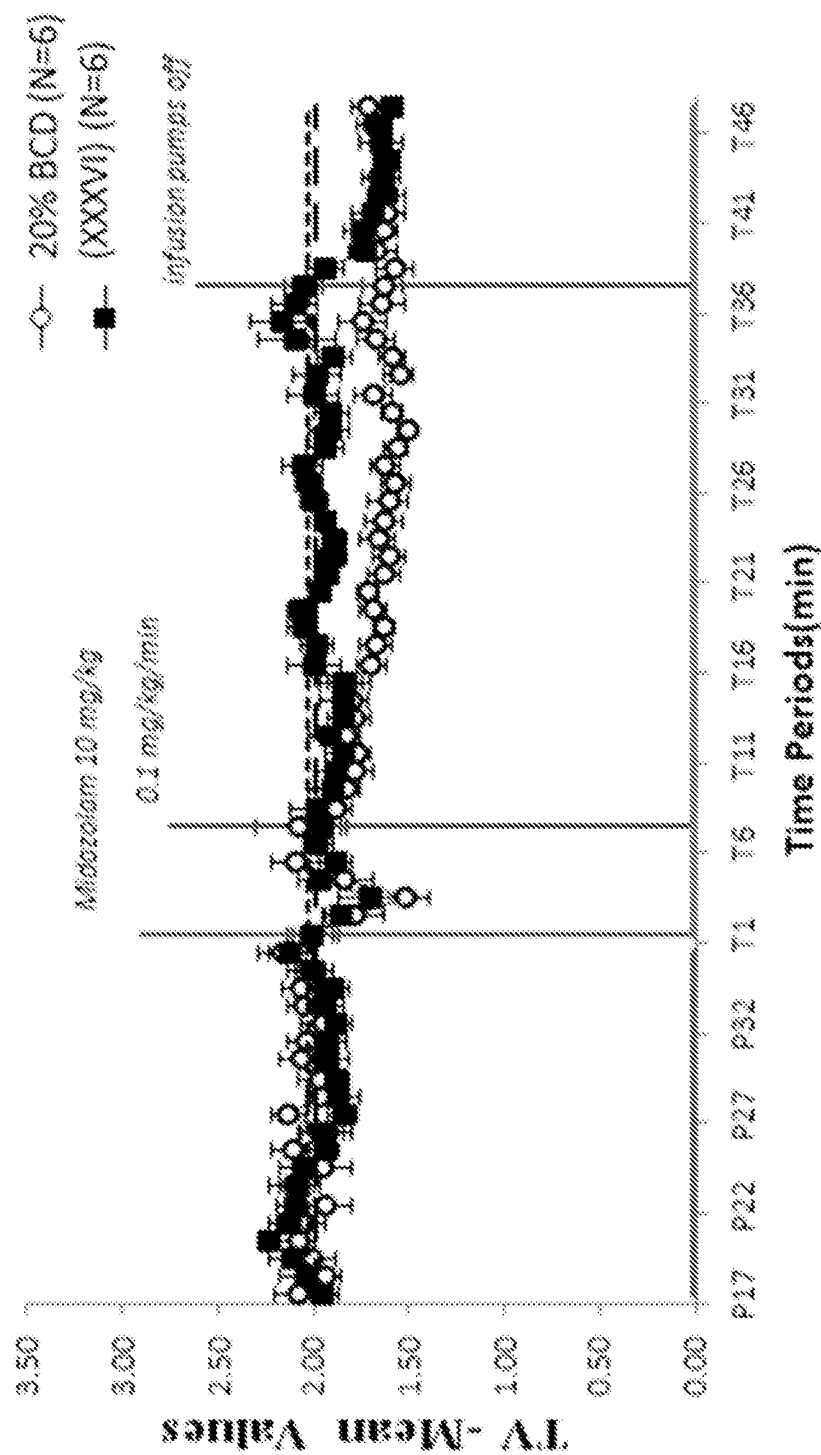


Fig. 17

Parameter: **f**

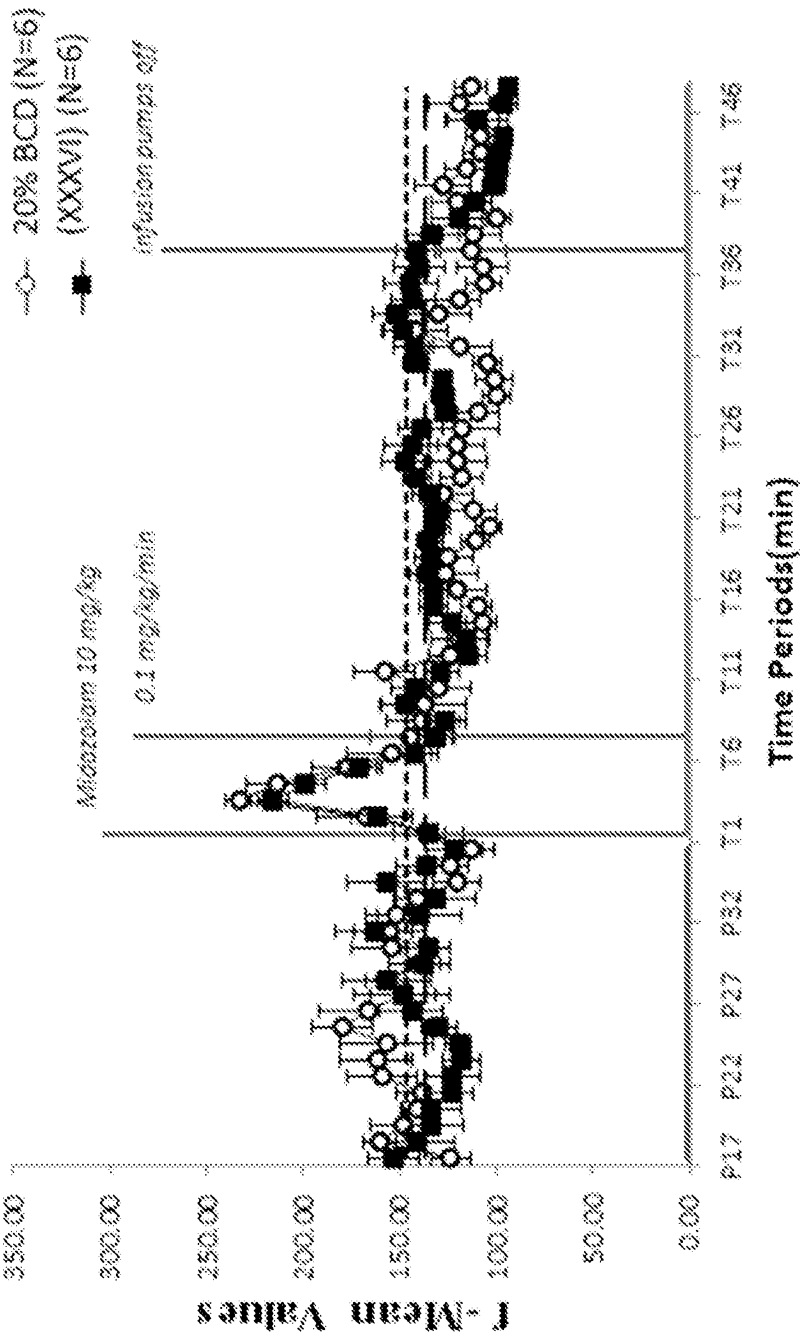


Fig. 18

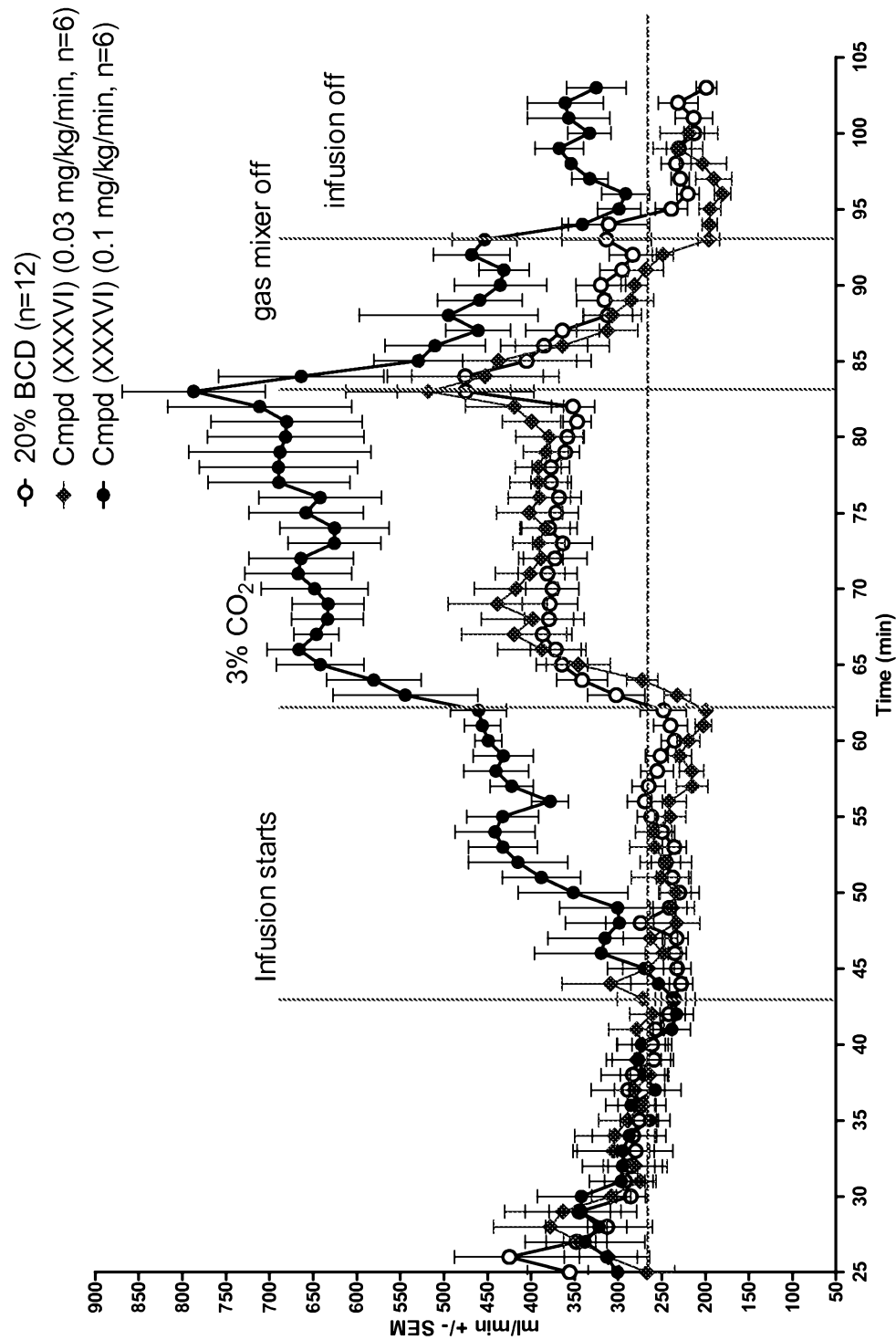


Fig. 19A

pH vs. (XXXXV) free base concentration (mg/mL)

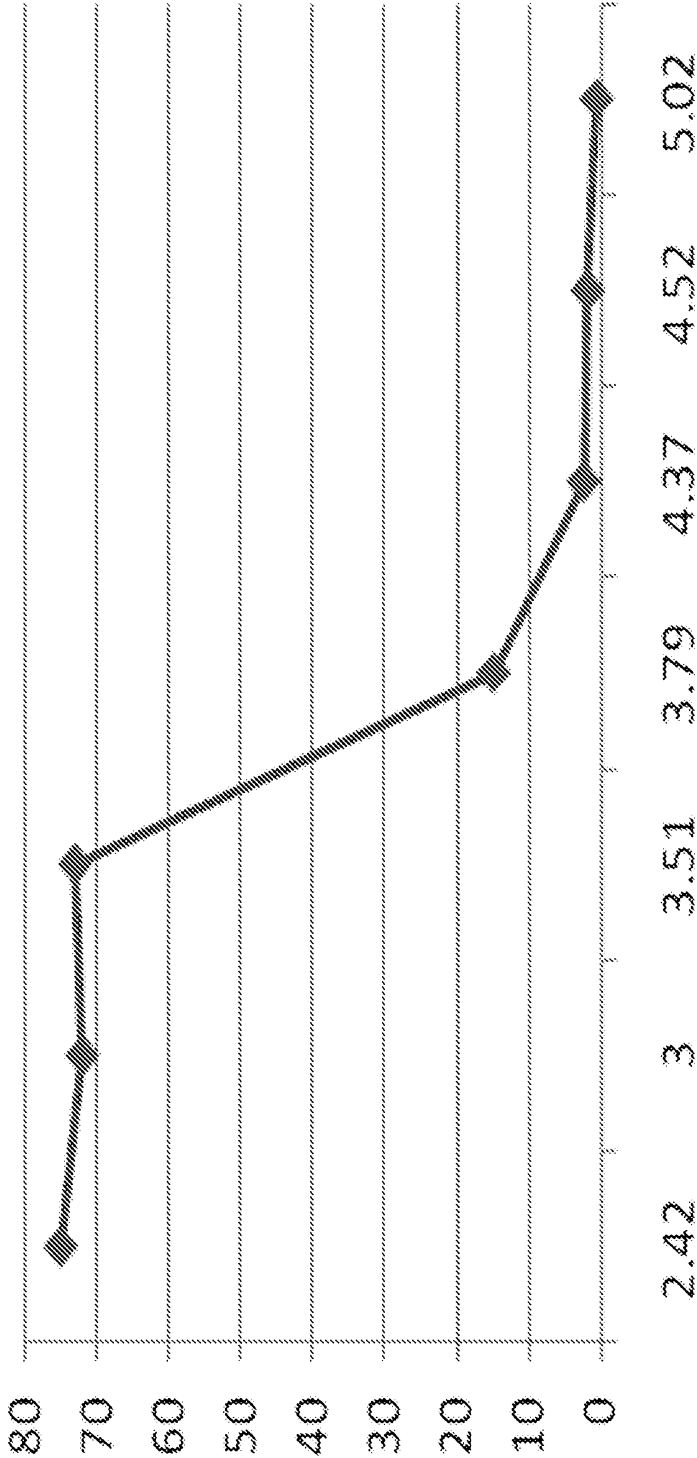


Fig. 19B
pH solubility Profile of (XXXXV)

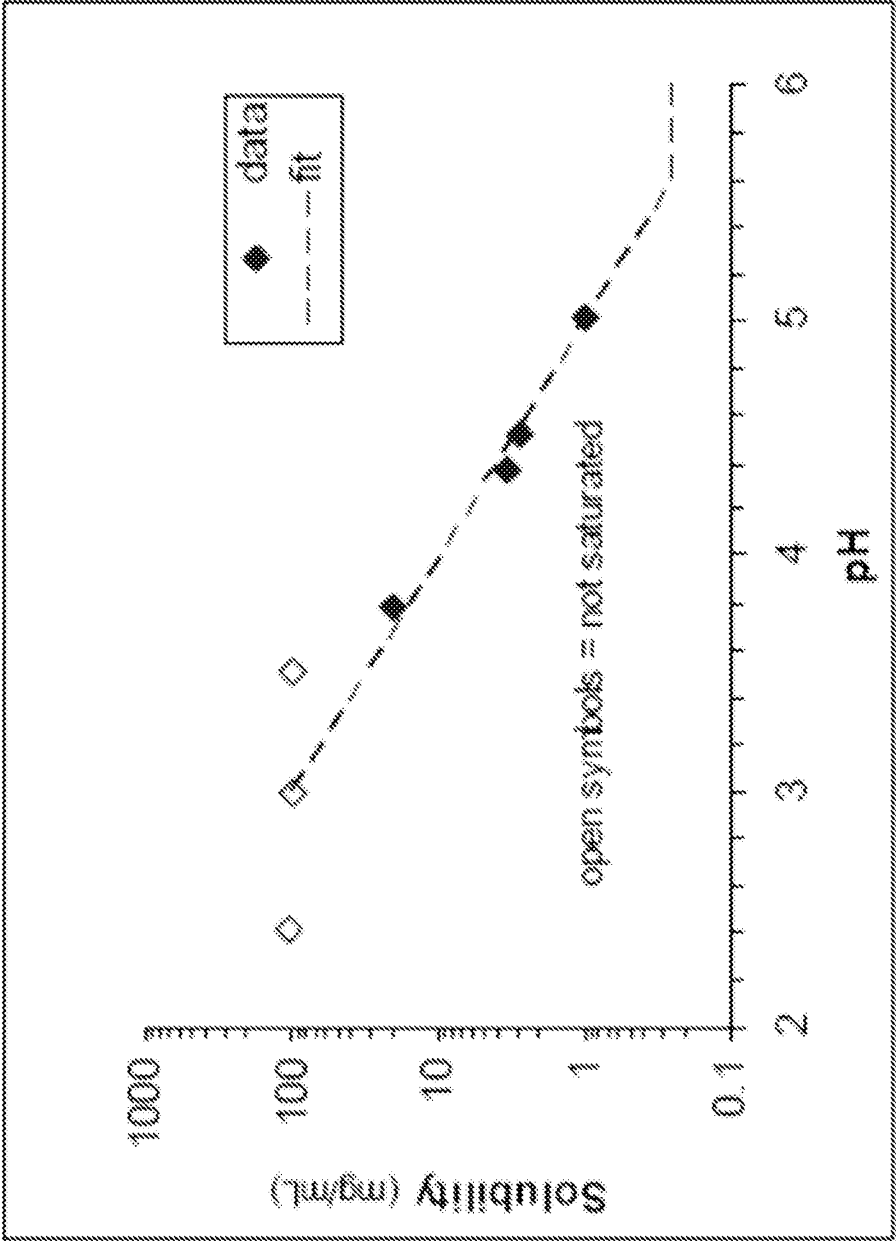


Fig. 20A

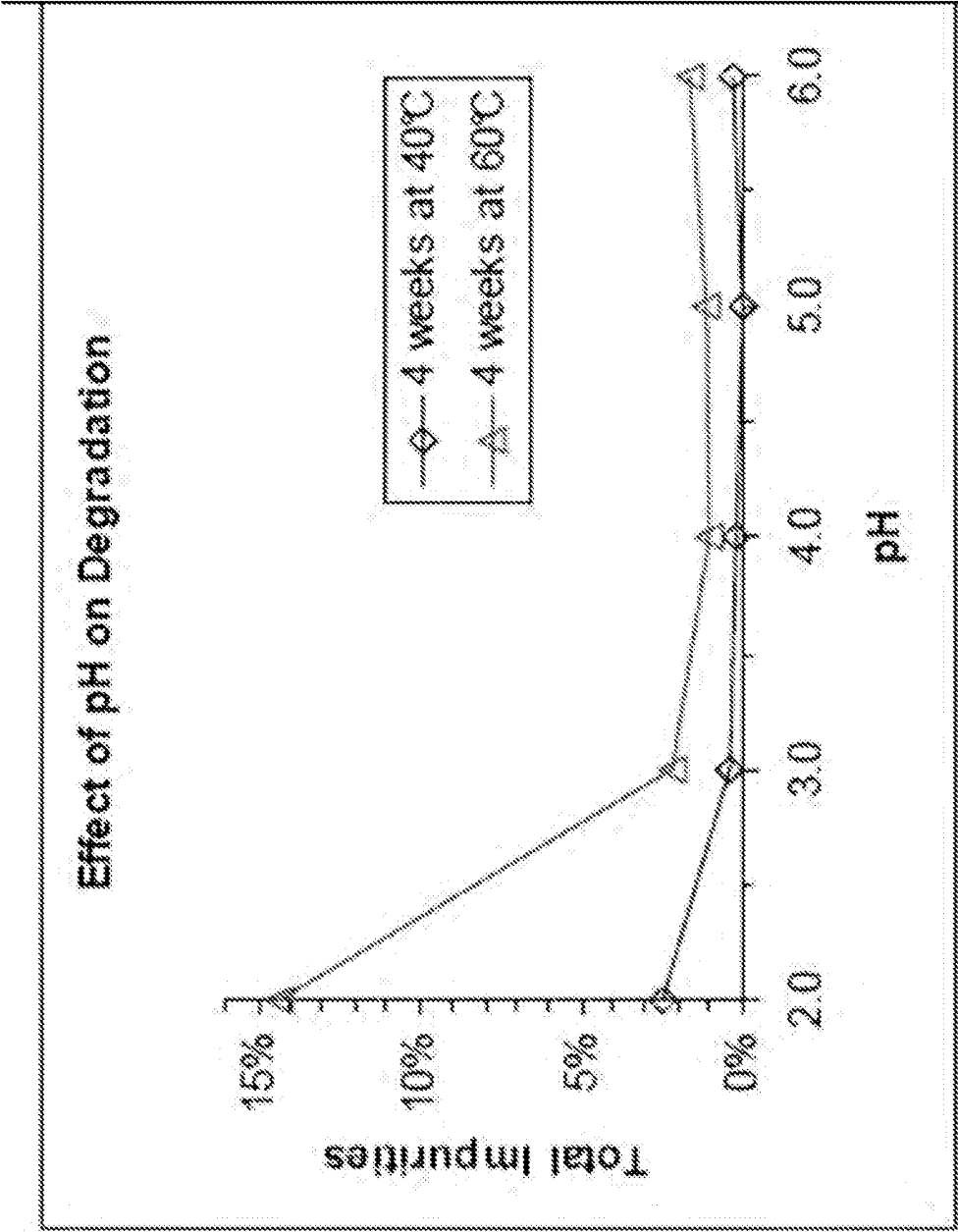


Fig. 20B

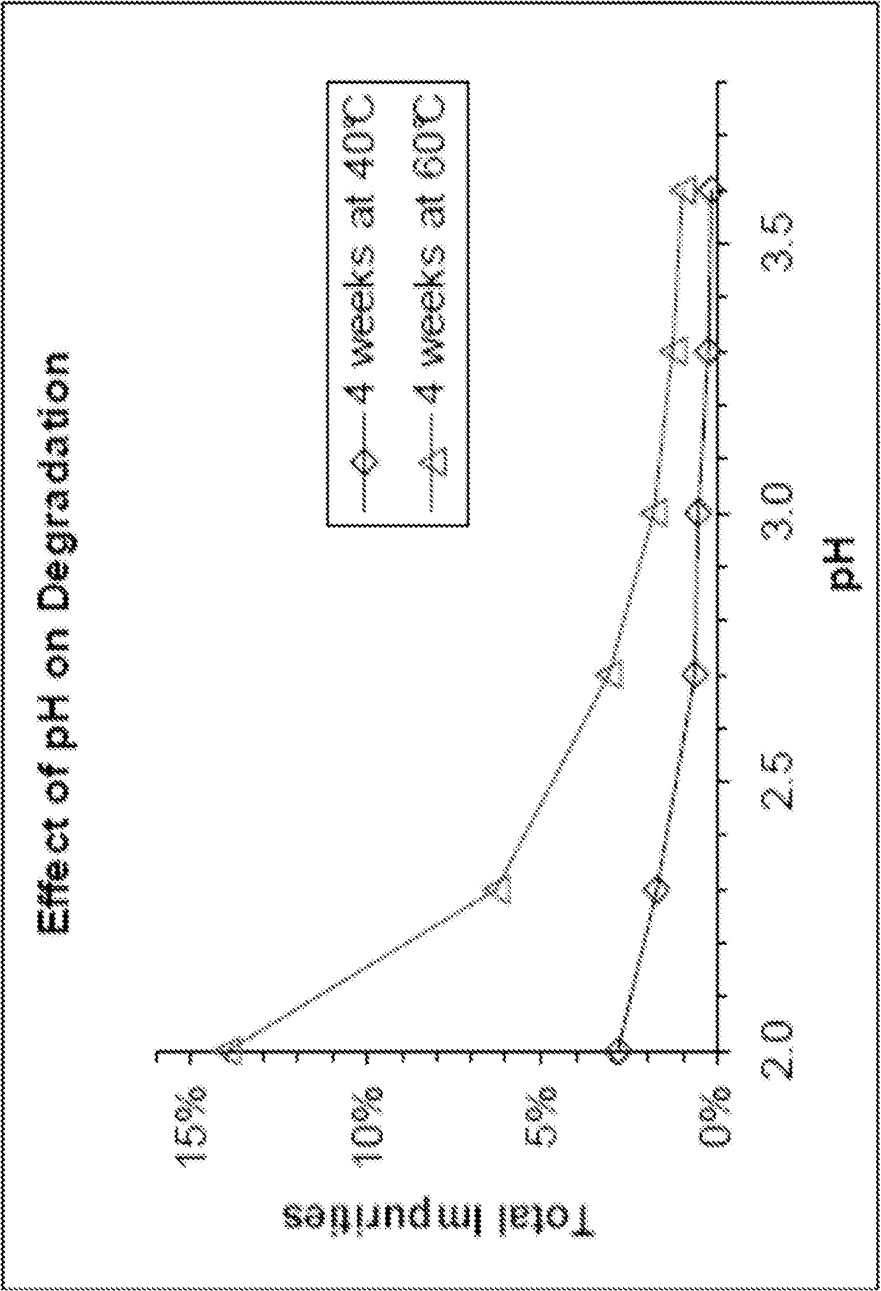


Fig. 21

Formation Kinetics of (CLXXVIII) impurity (RRT0.67)

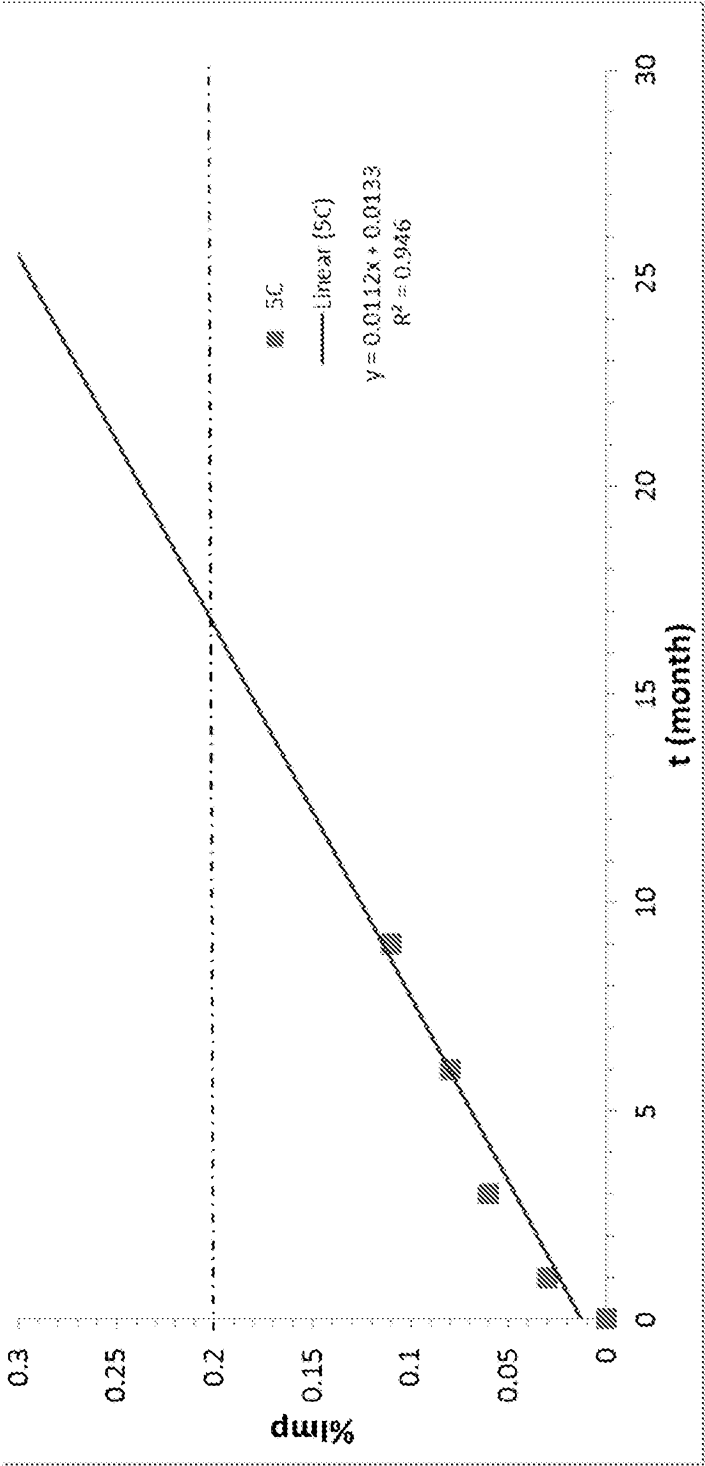


Fig. 22

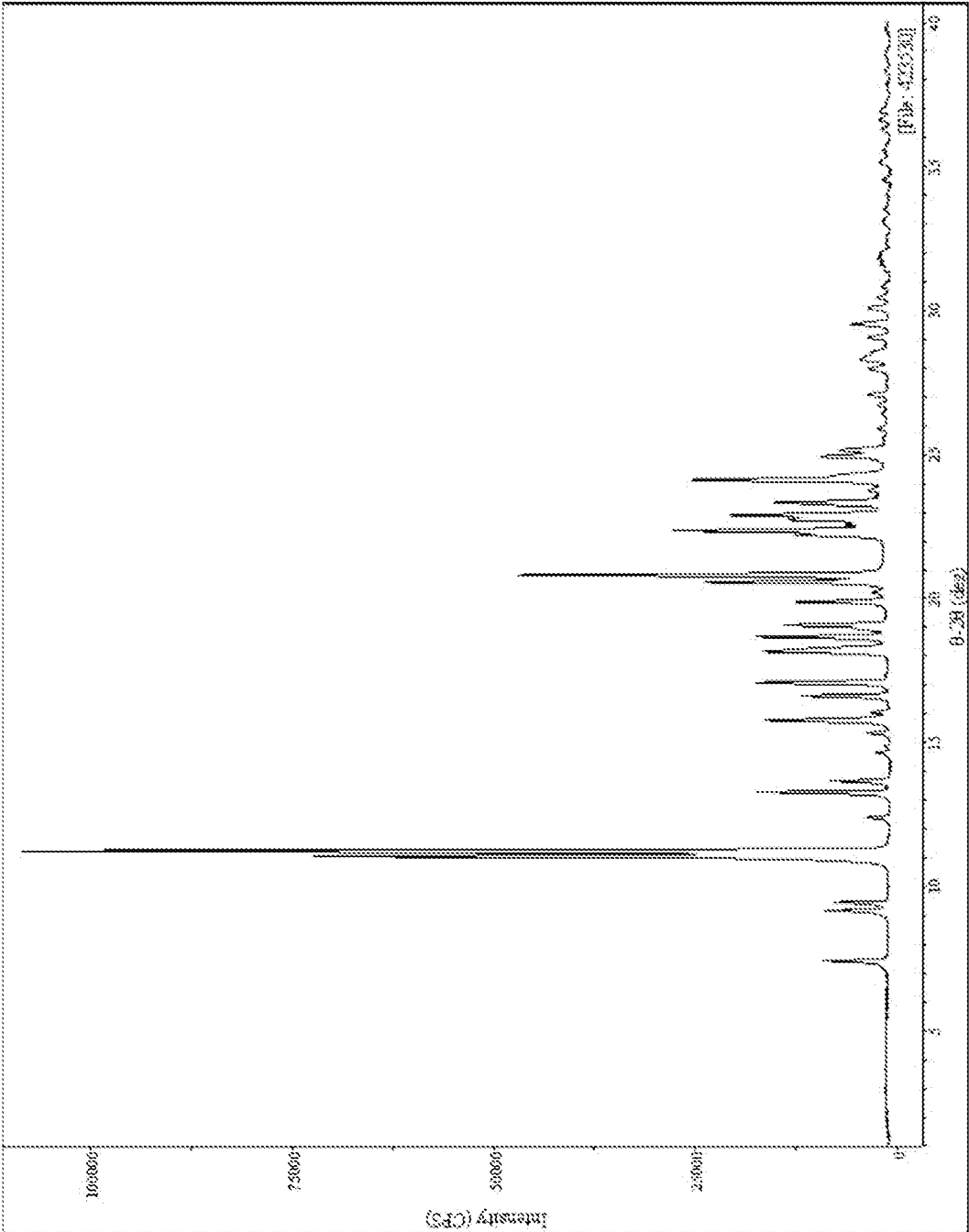


Fig. 23

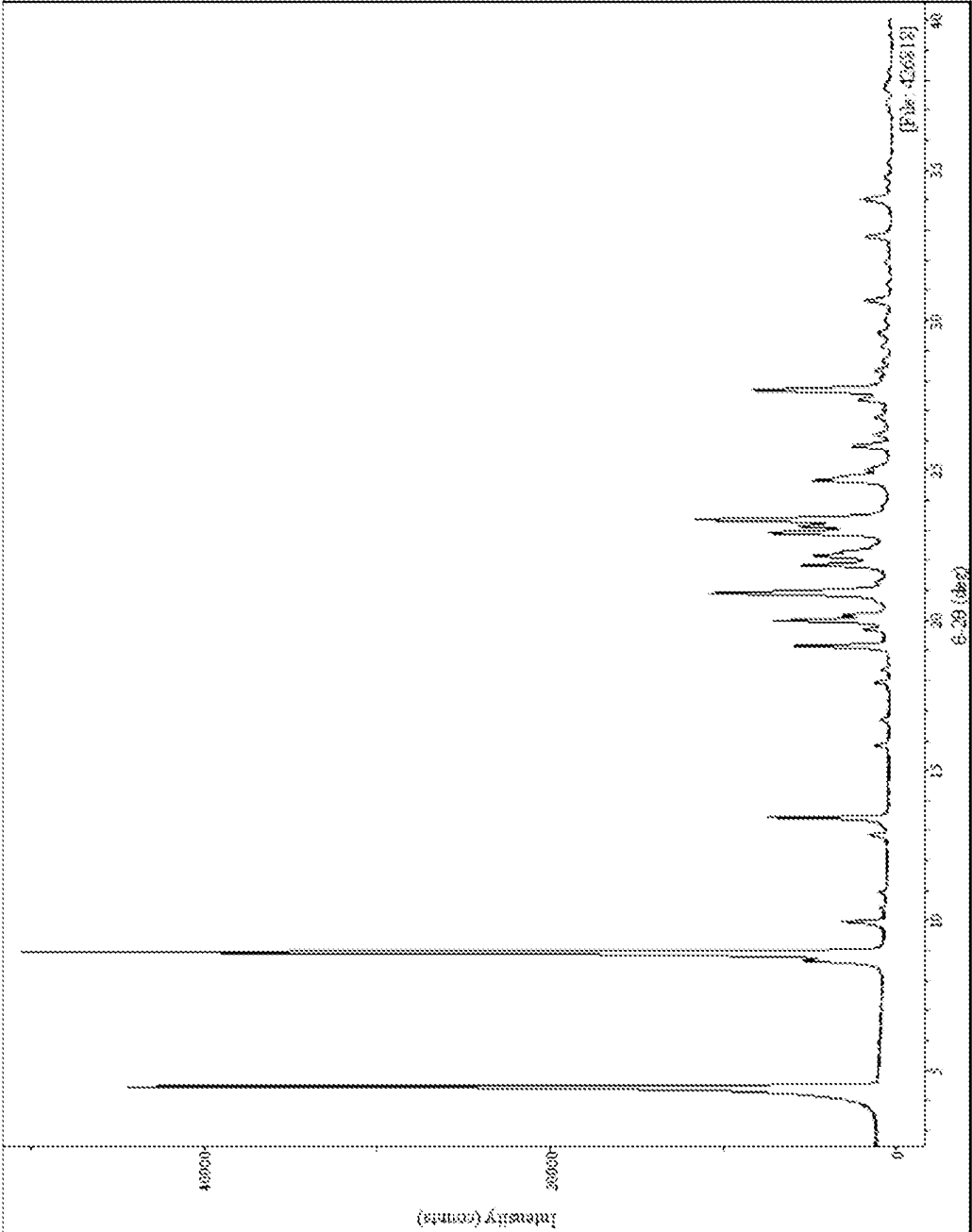


Fig. 24

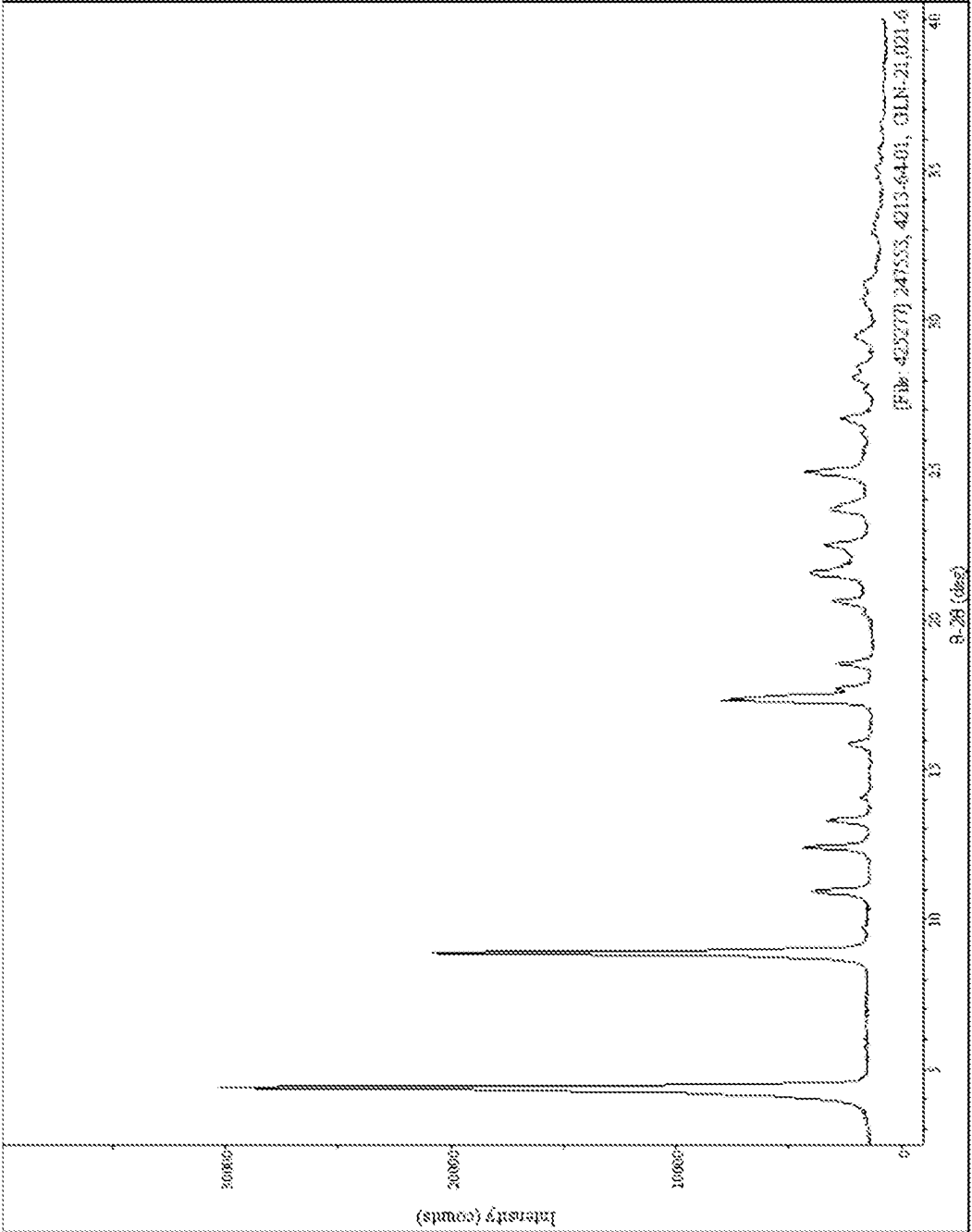


Fig. 25

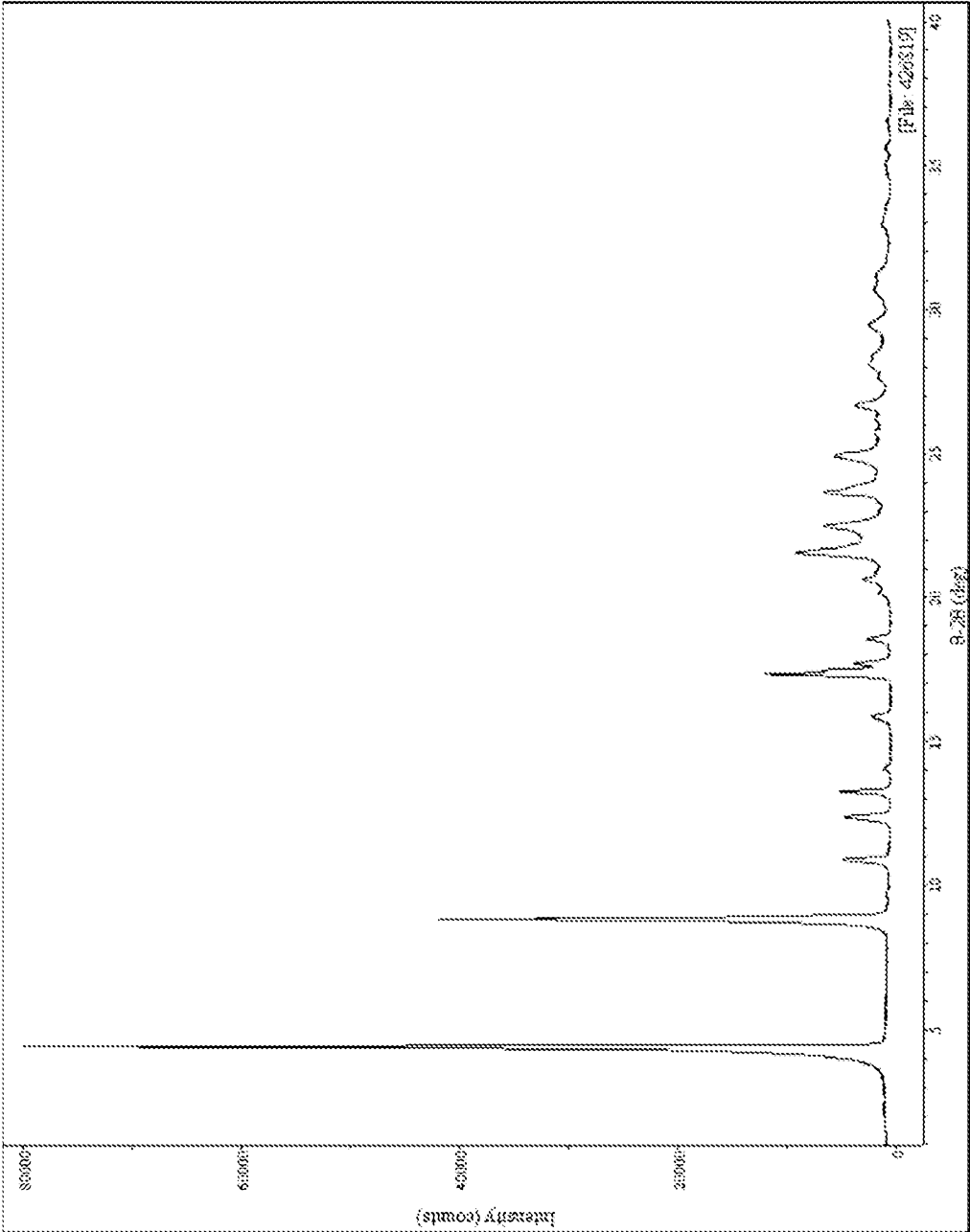


Fig. 26

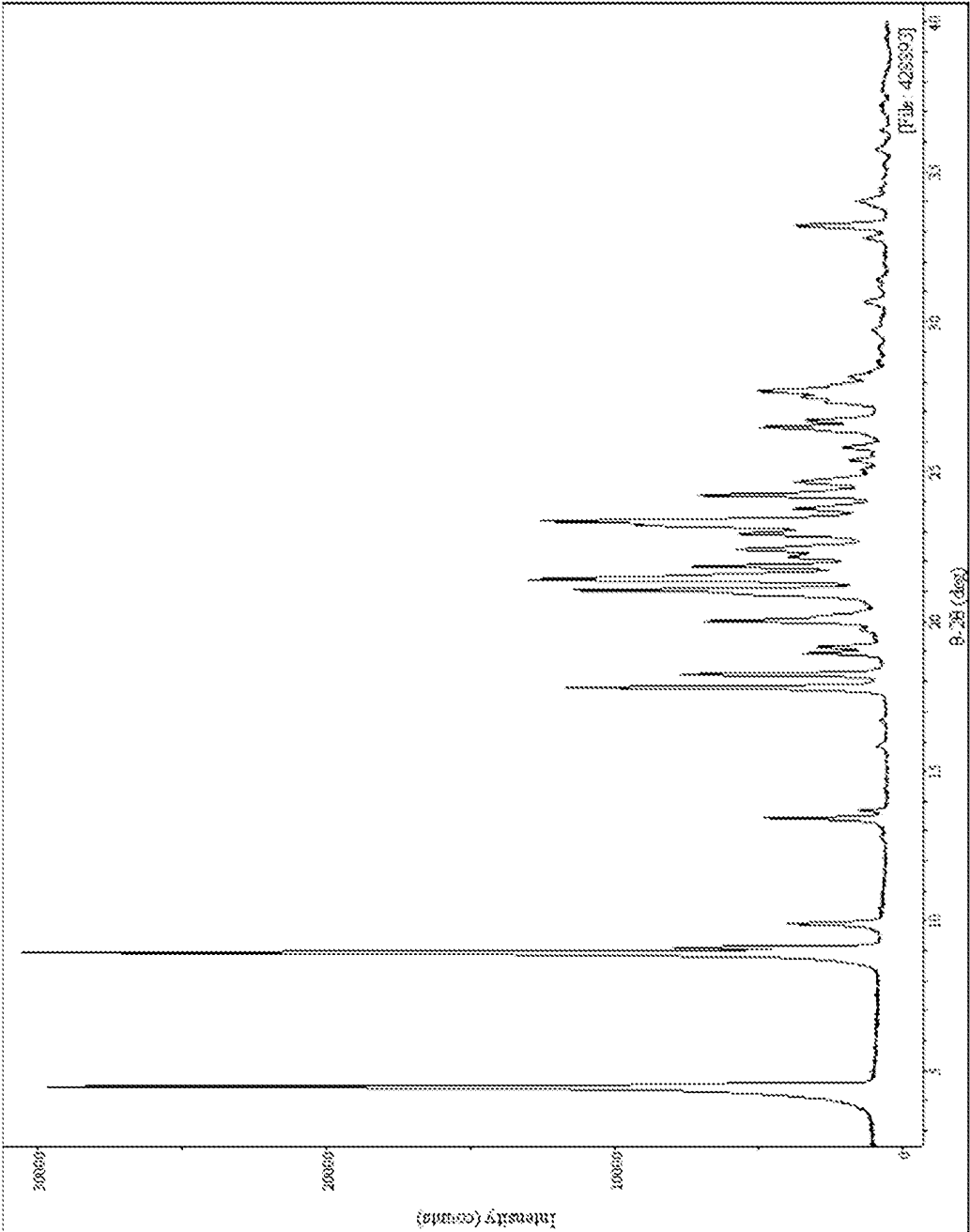


Fig. 27

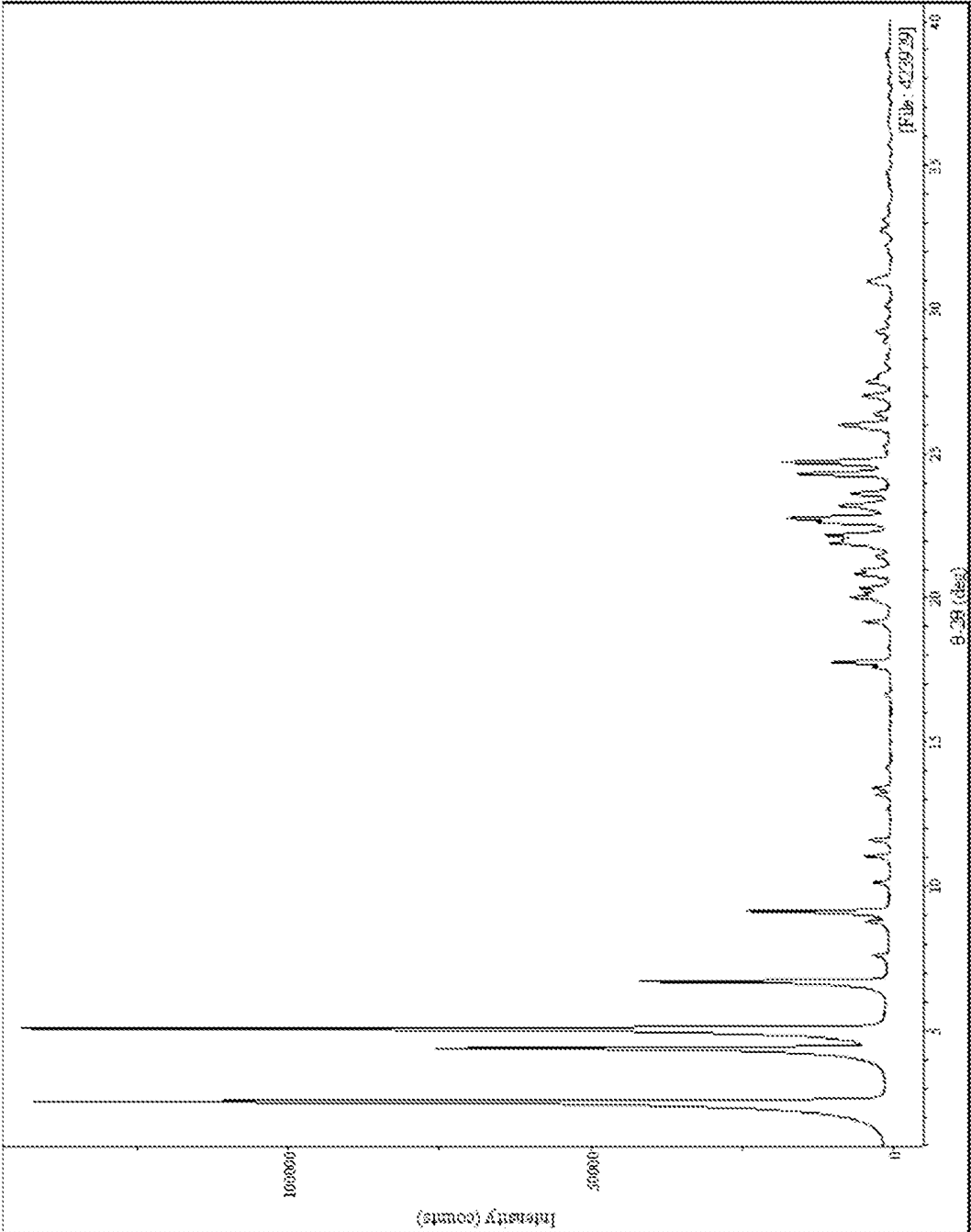


Fig. 28

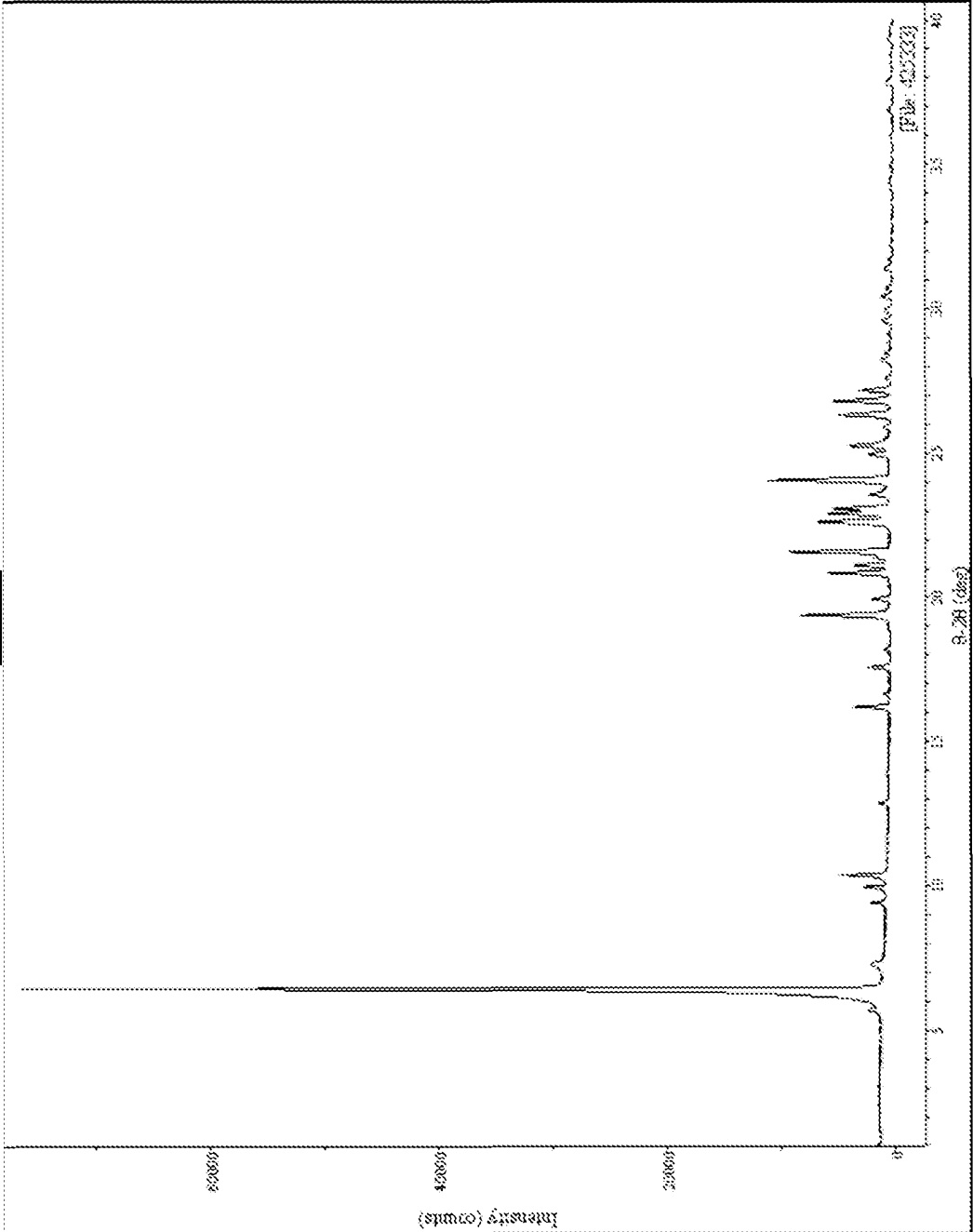


Fig. 29

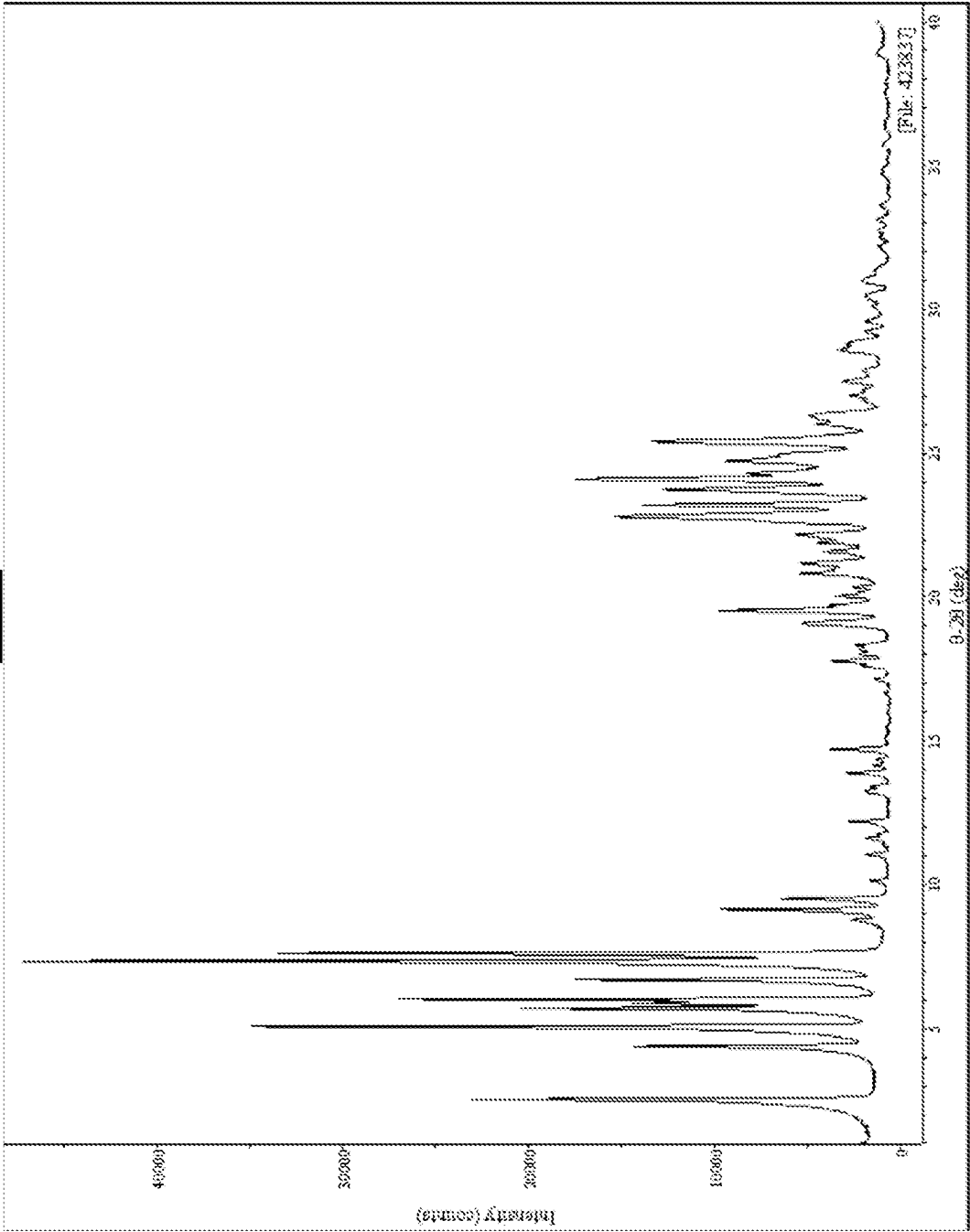


Fig. 30

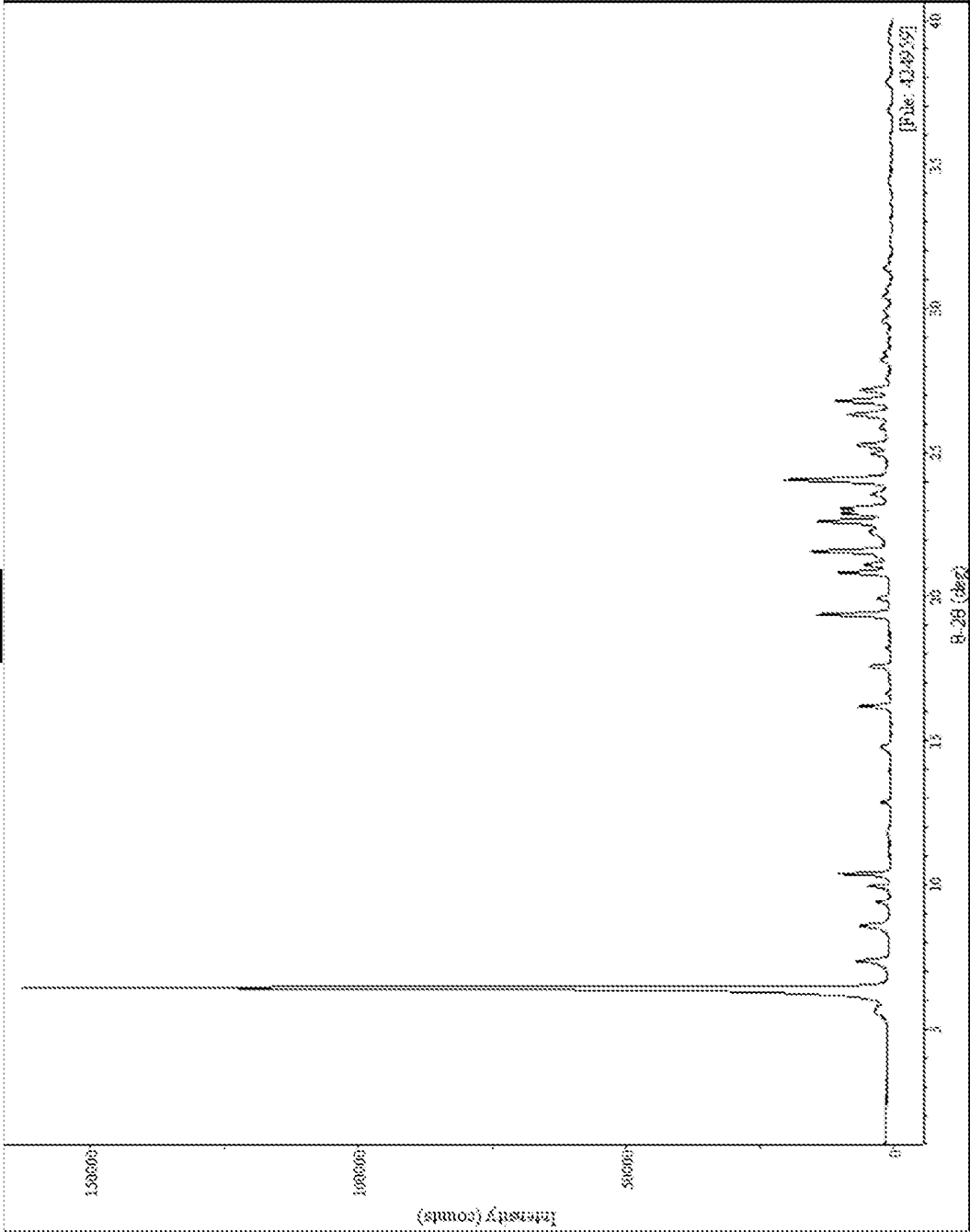


Fig. 31

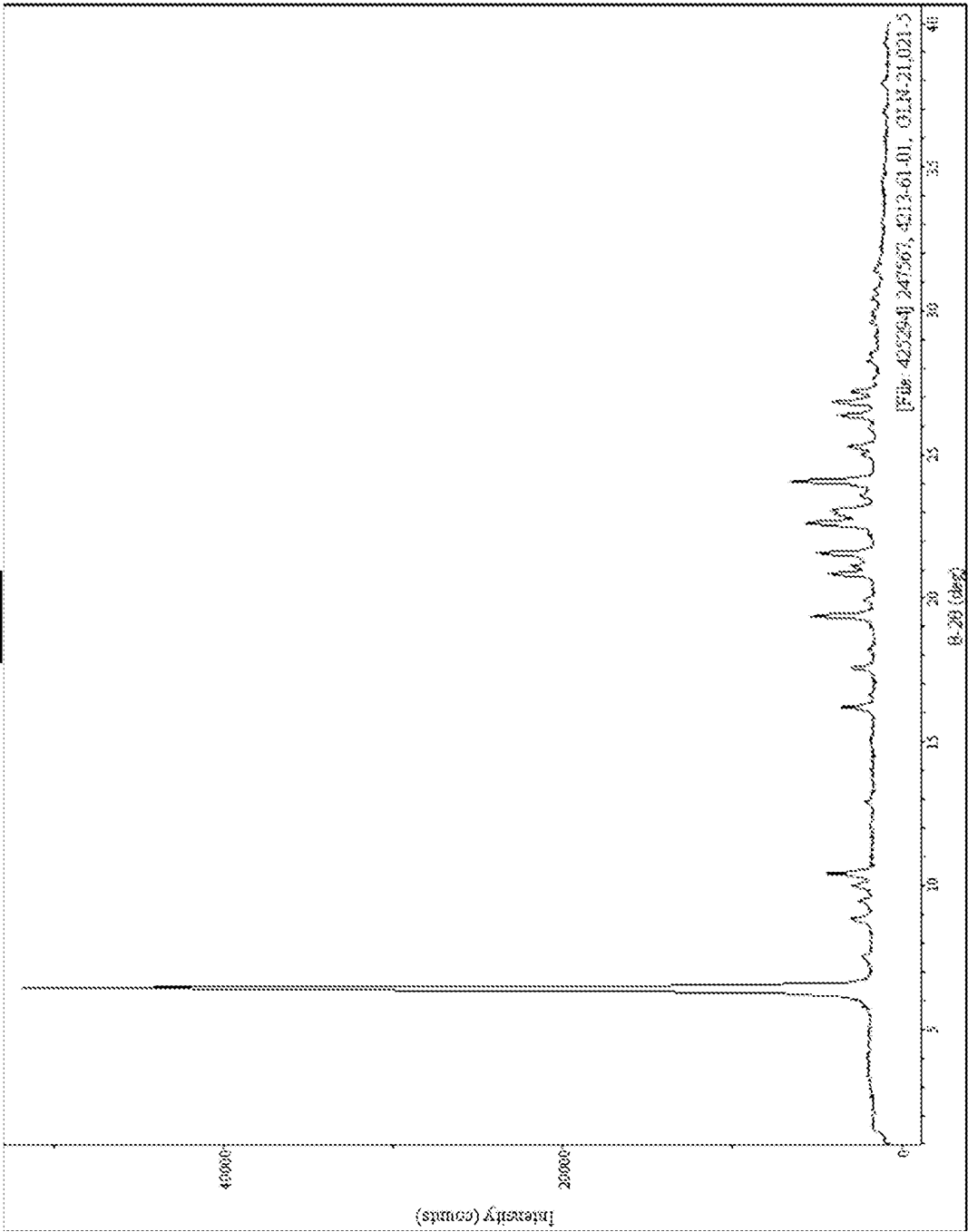


Fig. 32A

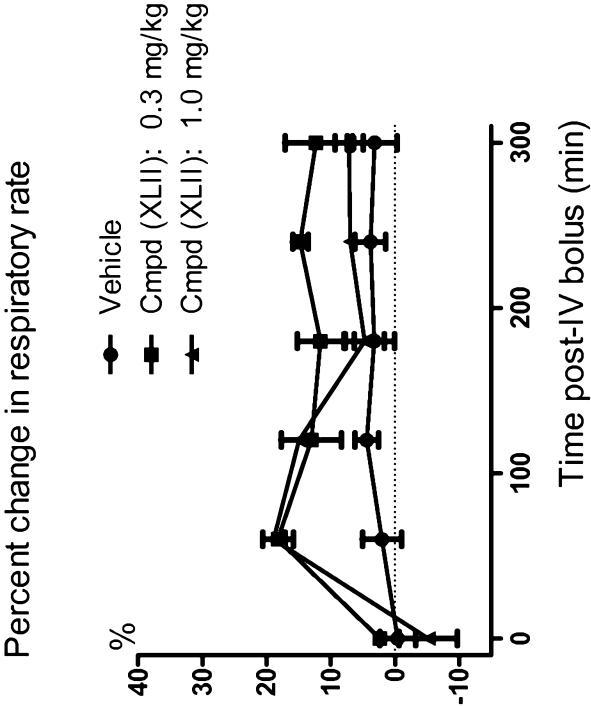


Fig. 32B

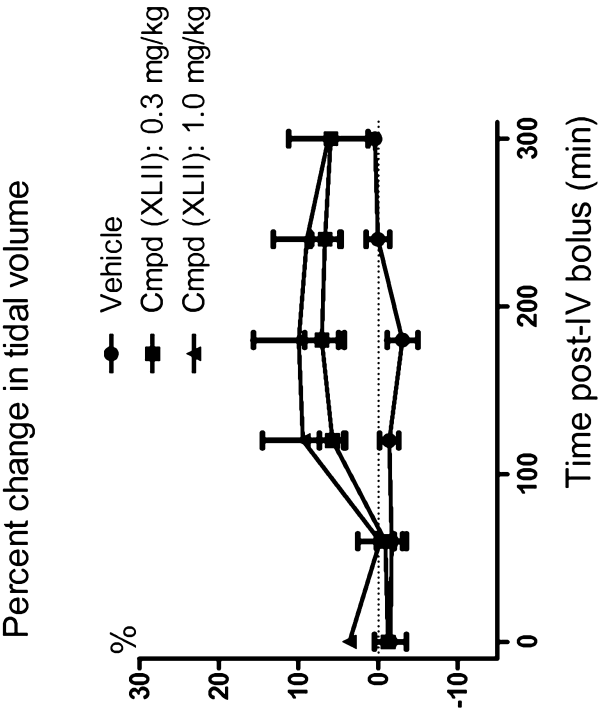


Fig. 32C

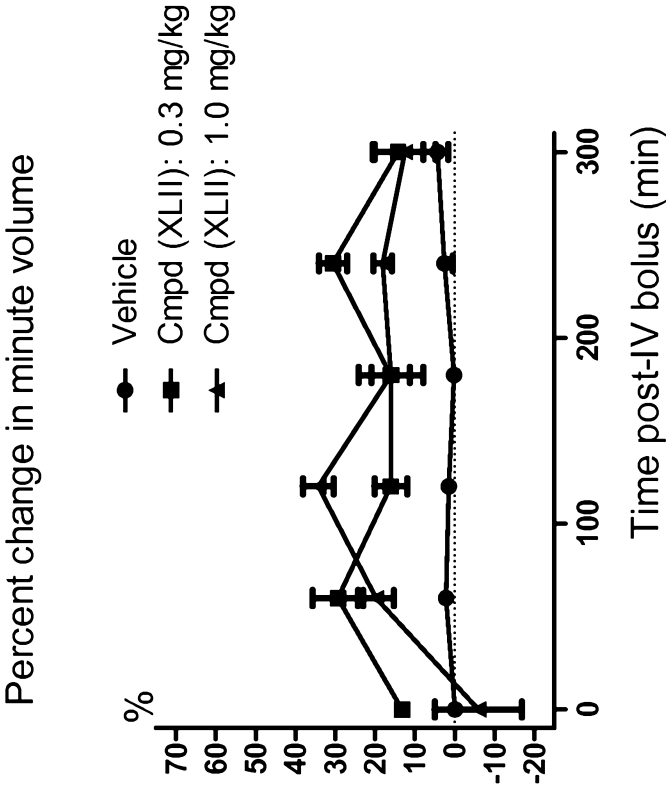


Fig. 32D

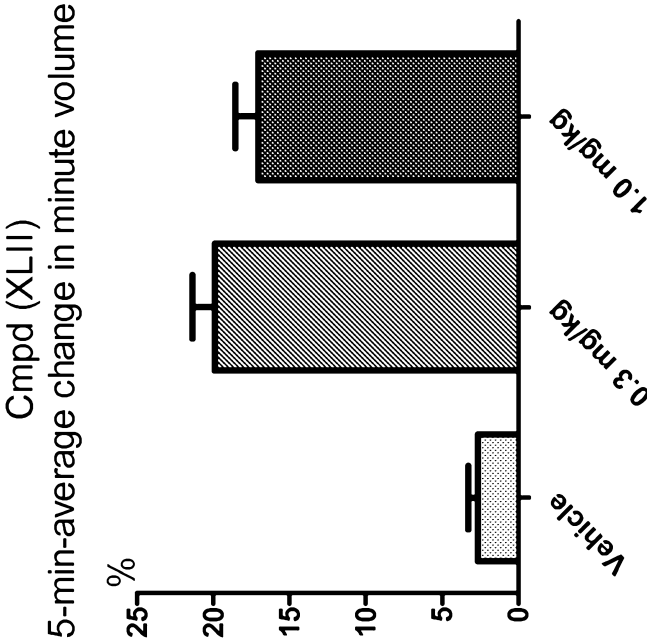


Fig. 33A

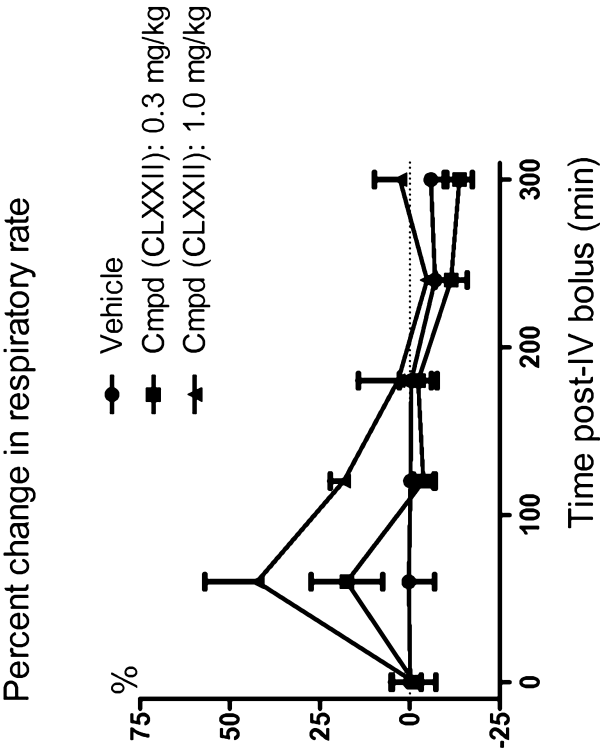


Fig. 33B

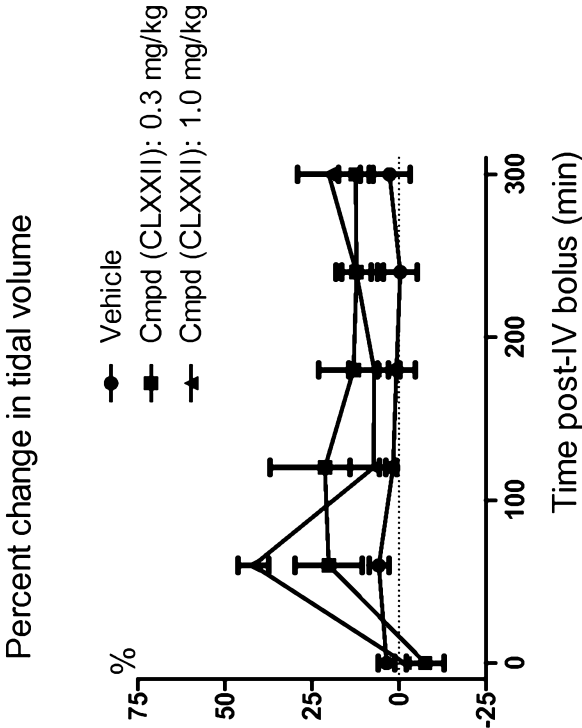


Fig. 33C

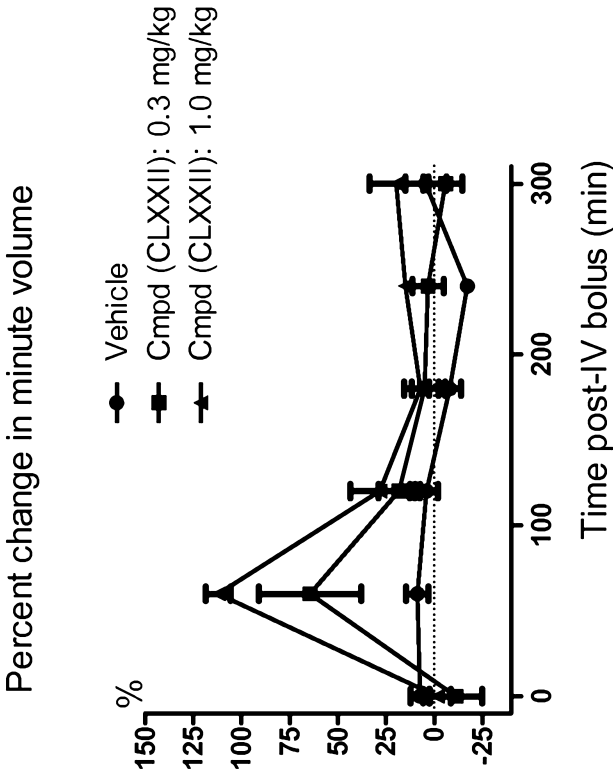


Fig. 33D

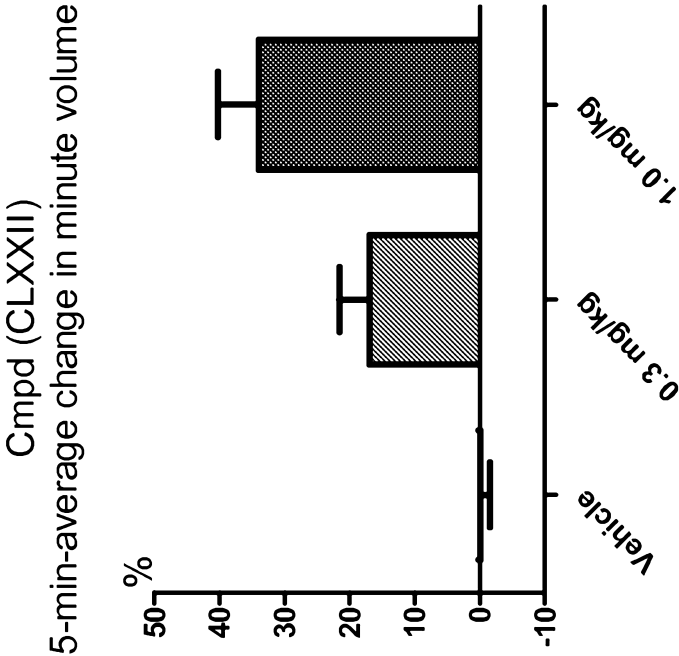


Fig. 34

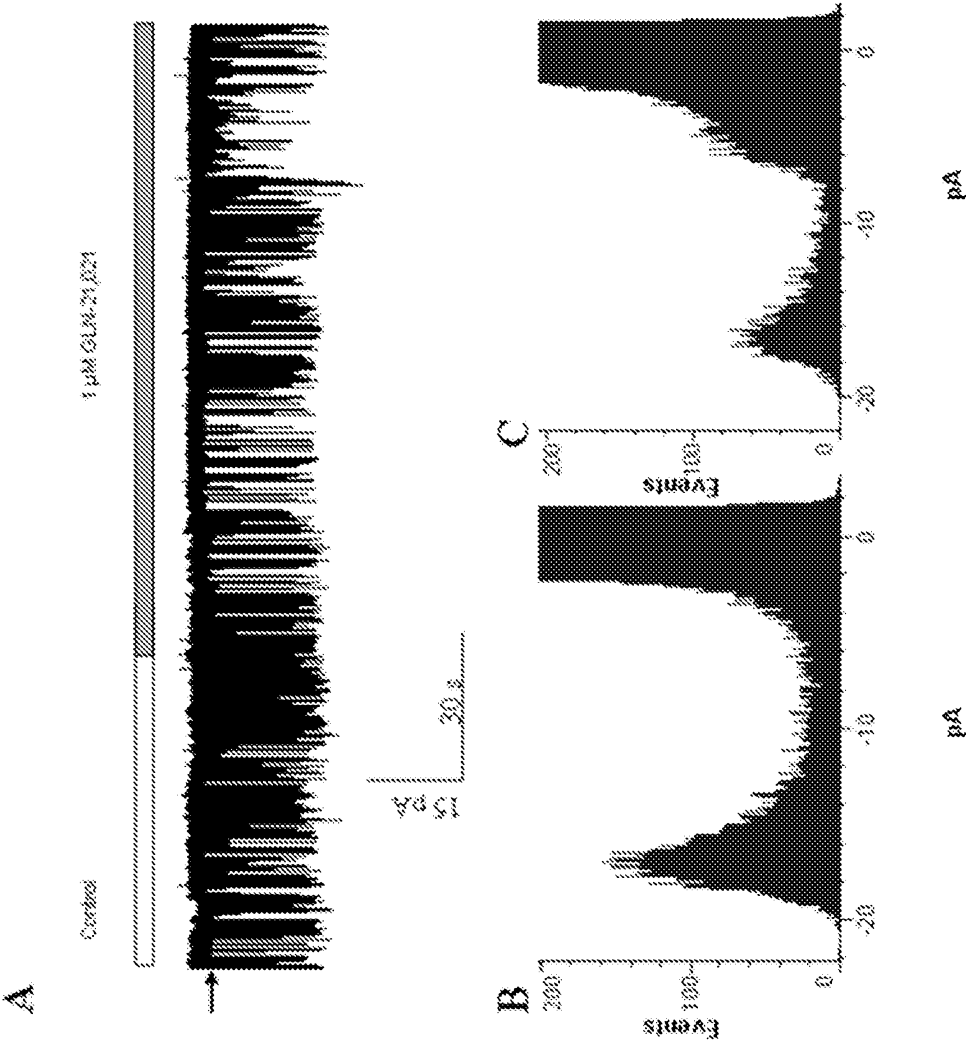


Fig. 35

Period	Dose
1	0.1 mg/kg/h x 1 h
2	0.3 mg/kg/h x 1 h
3	0.3 mg/kg/h x 1 h
4	0.6 mg/kg/h x 1 h
5	0.95 mg/kg/h x 1 h
6	0.72 mg/kg/h x 2 h
7	0.72 mg/kg/h x 3 h
8	0.54 mg/kg/h x 4 h
9	0.72/0.36 mg/kg/h x 1/3 h
- group 1	- group 2
	- group 3

Fig. 36

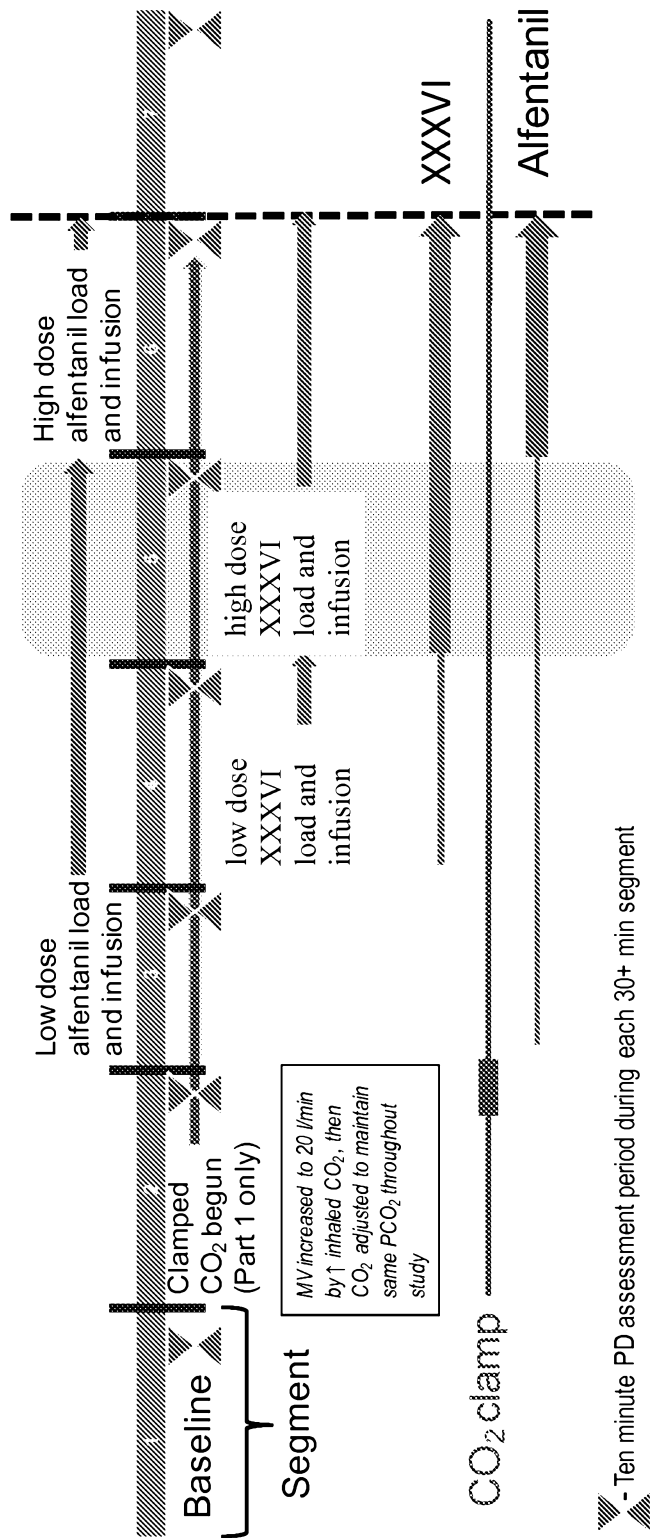


Fig. 37

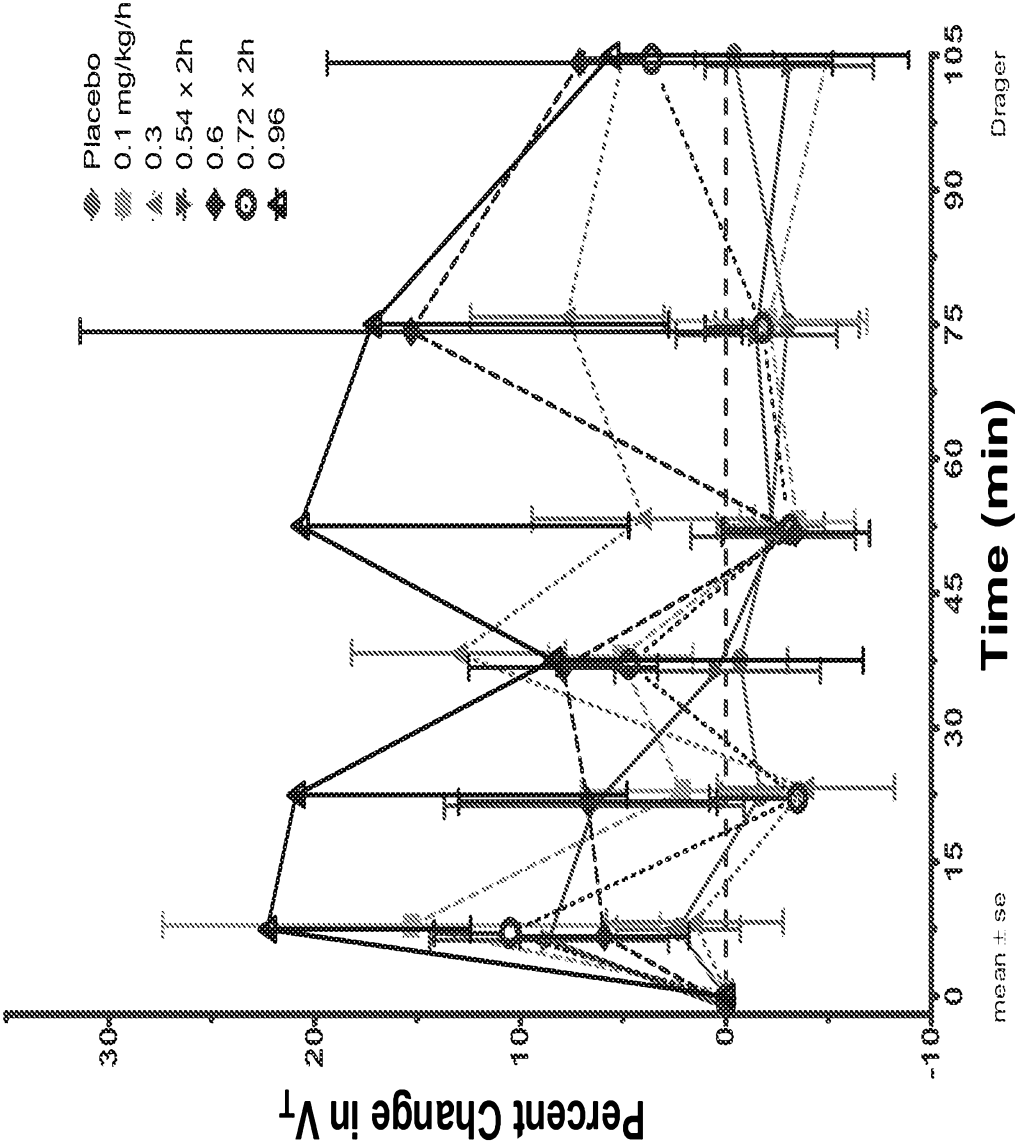
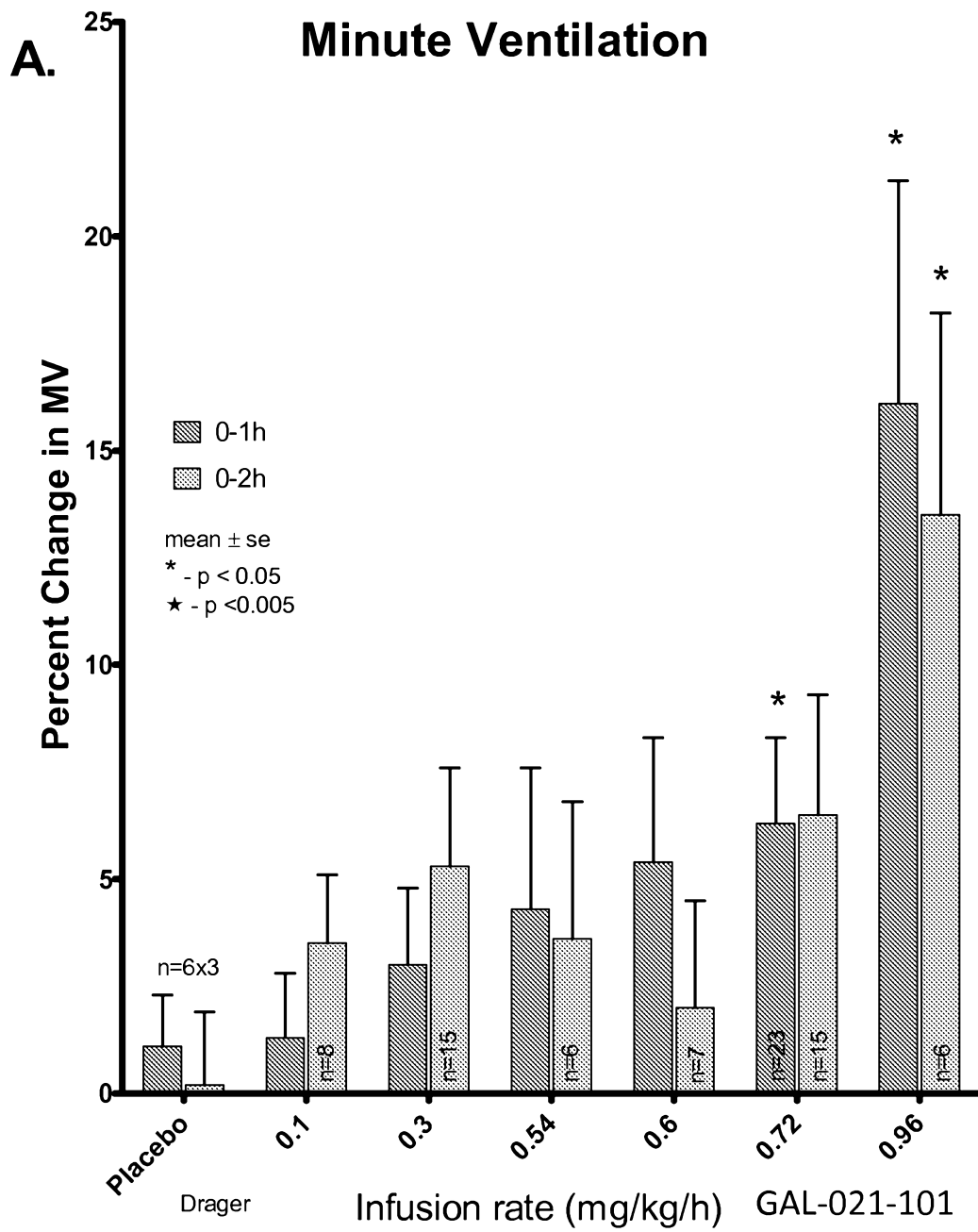


Fig. 38A

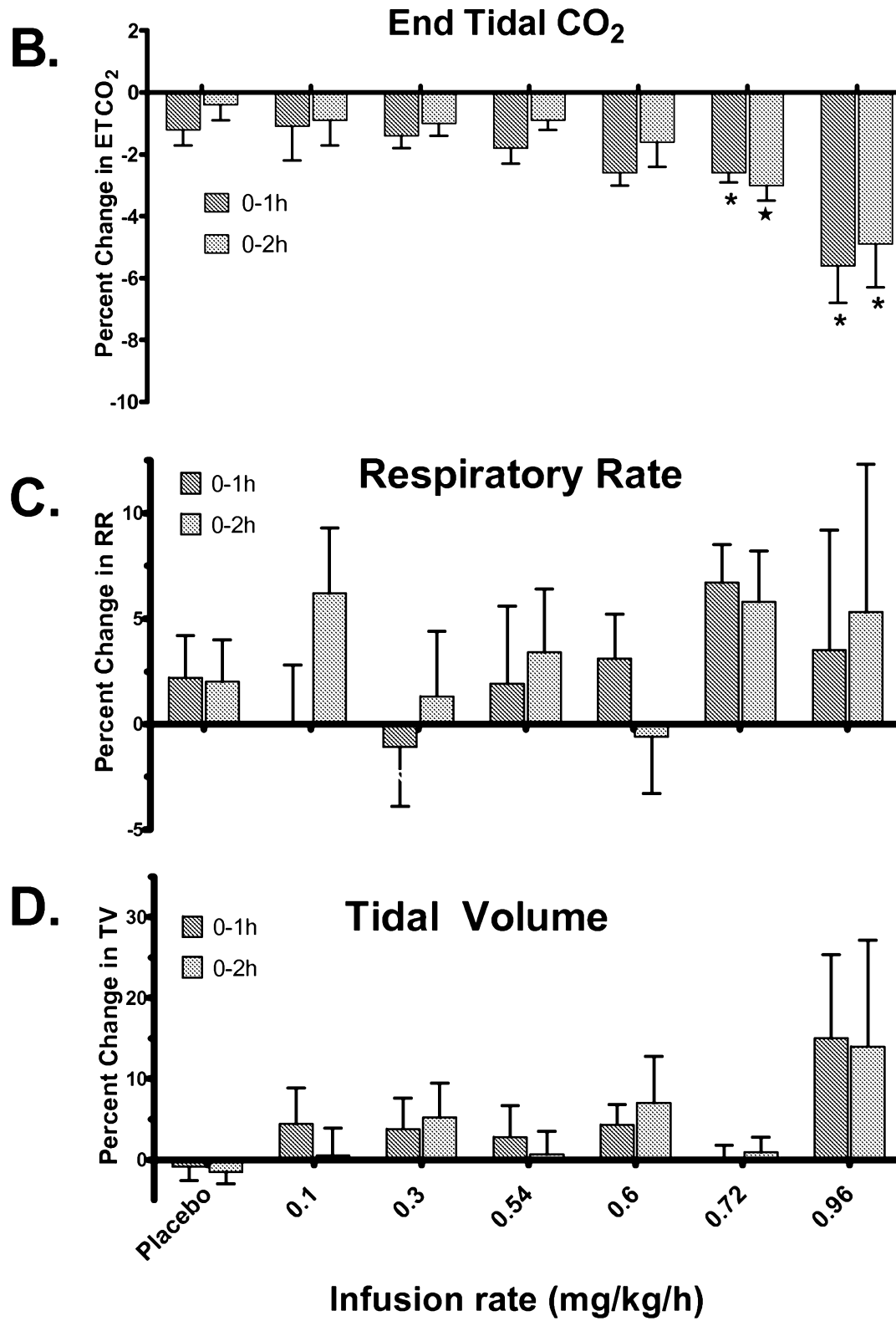
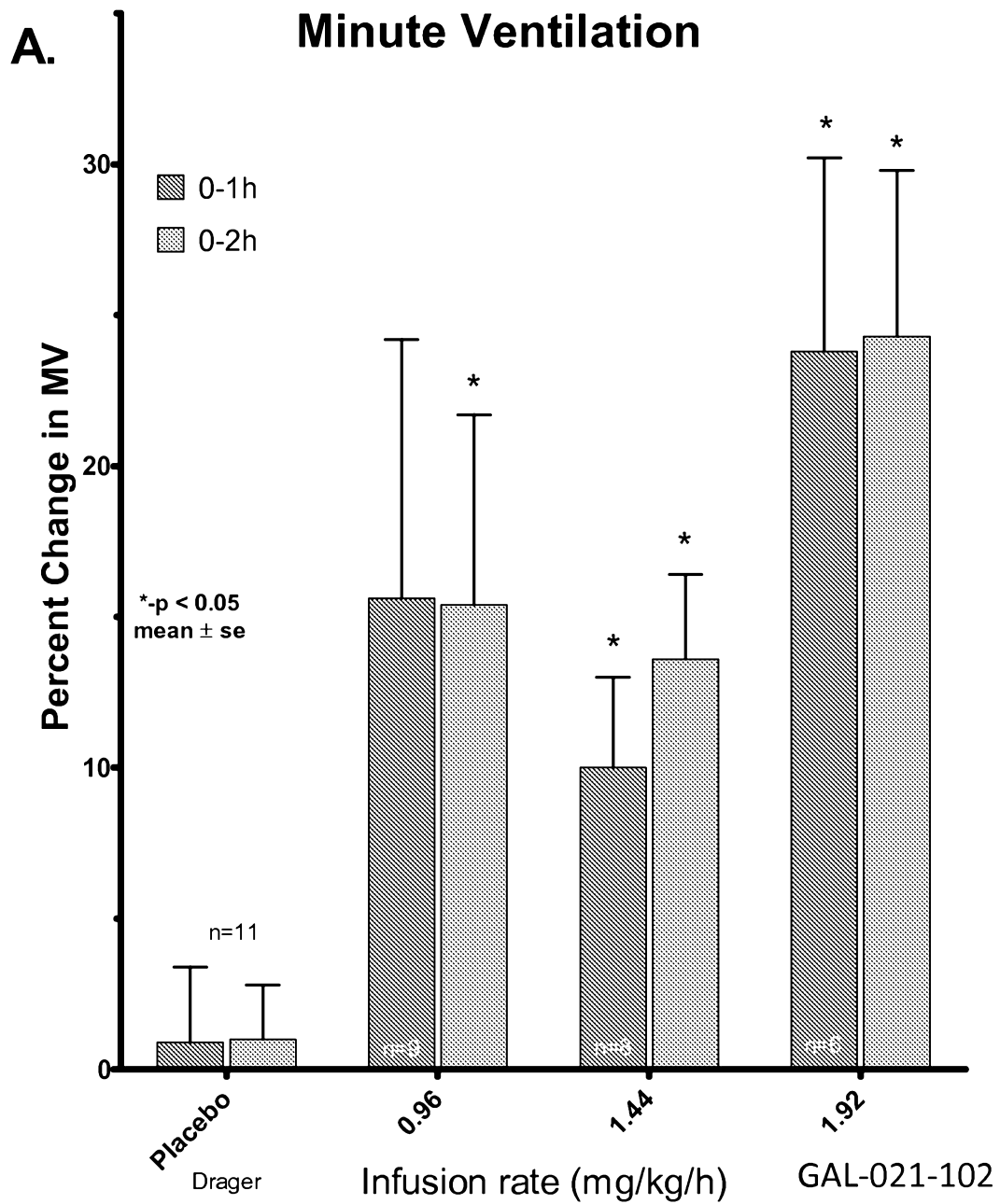
Figs. 38B-D

Fig. 39A

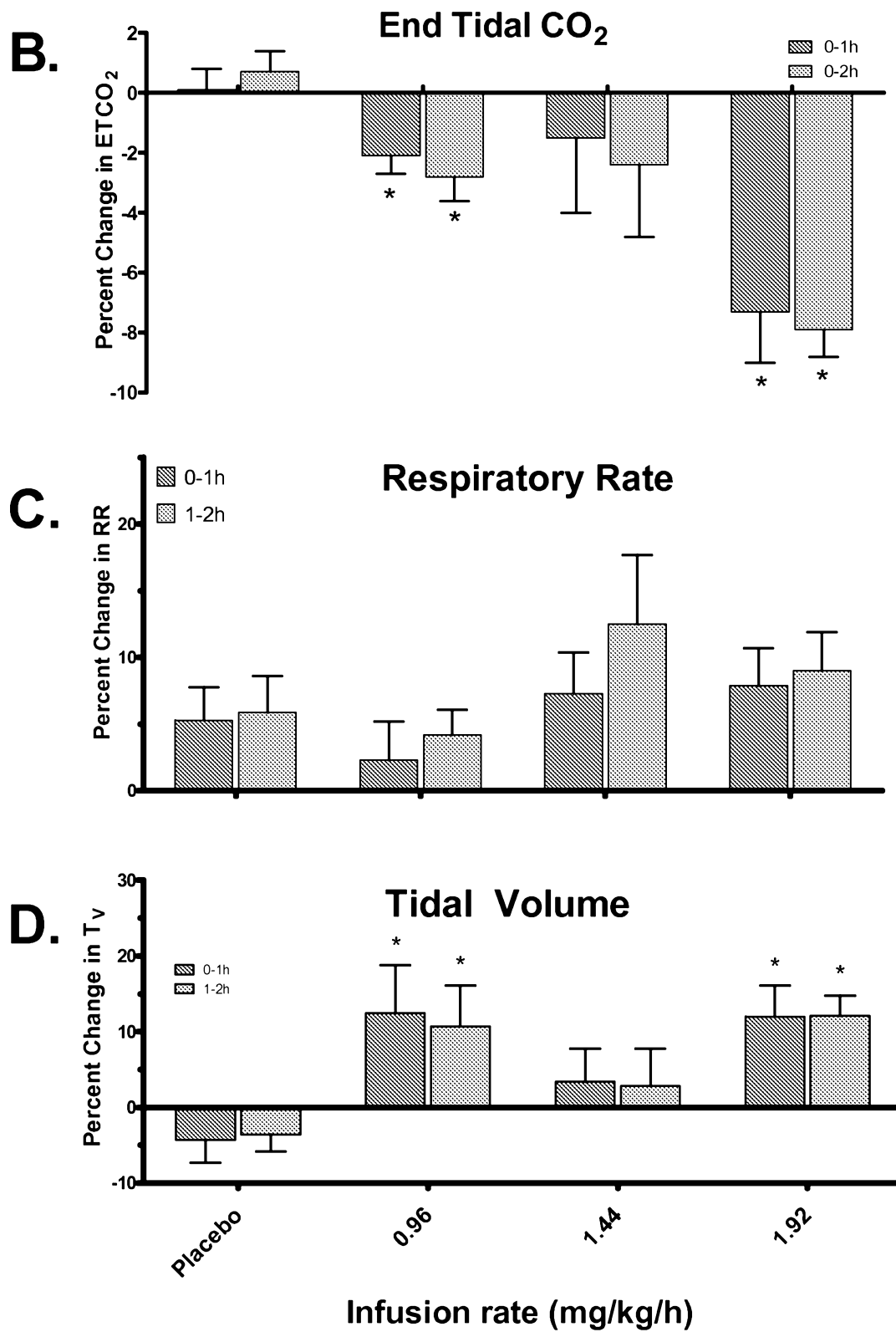
Figs. 39B-D

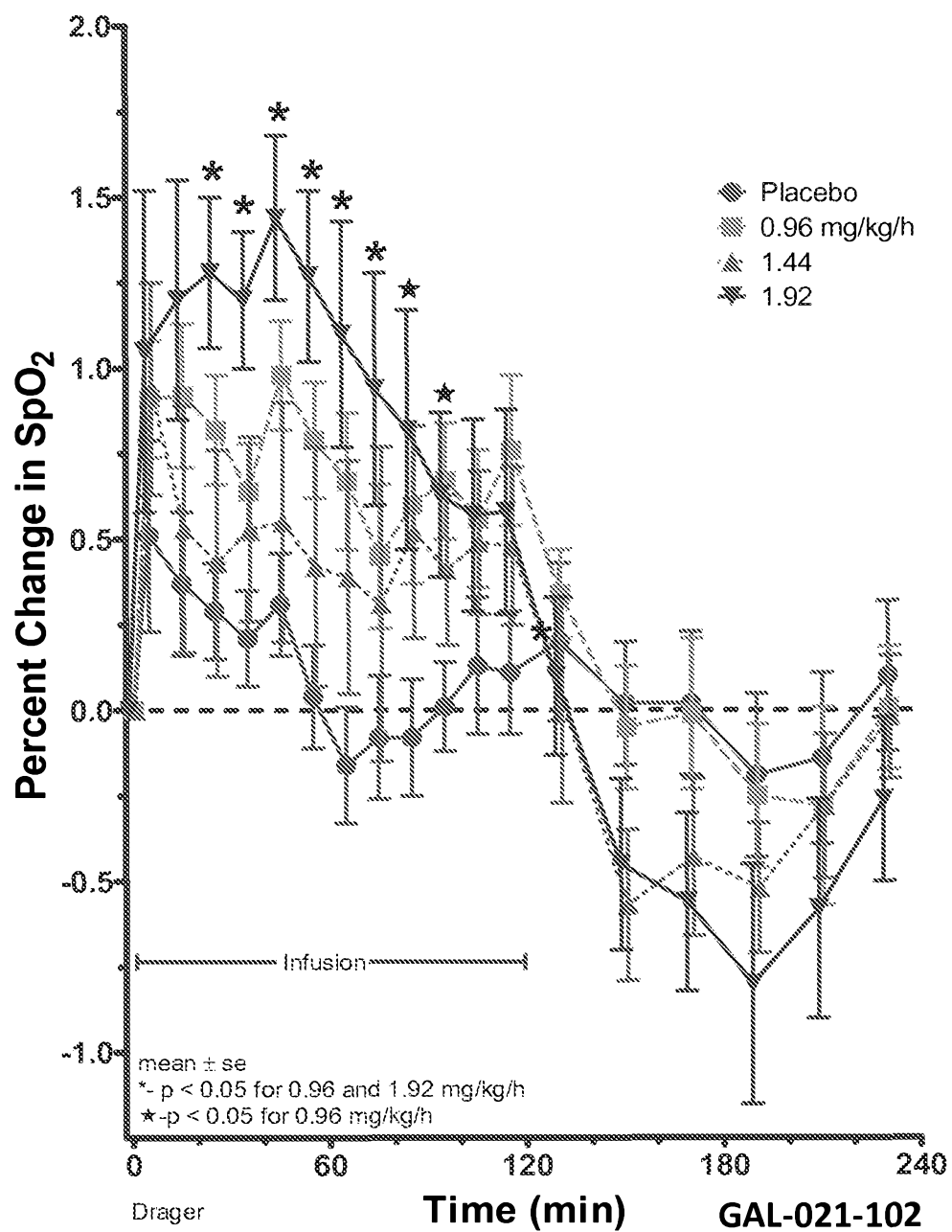
Fig. 40

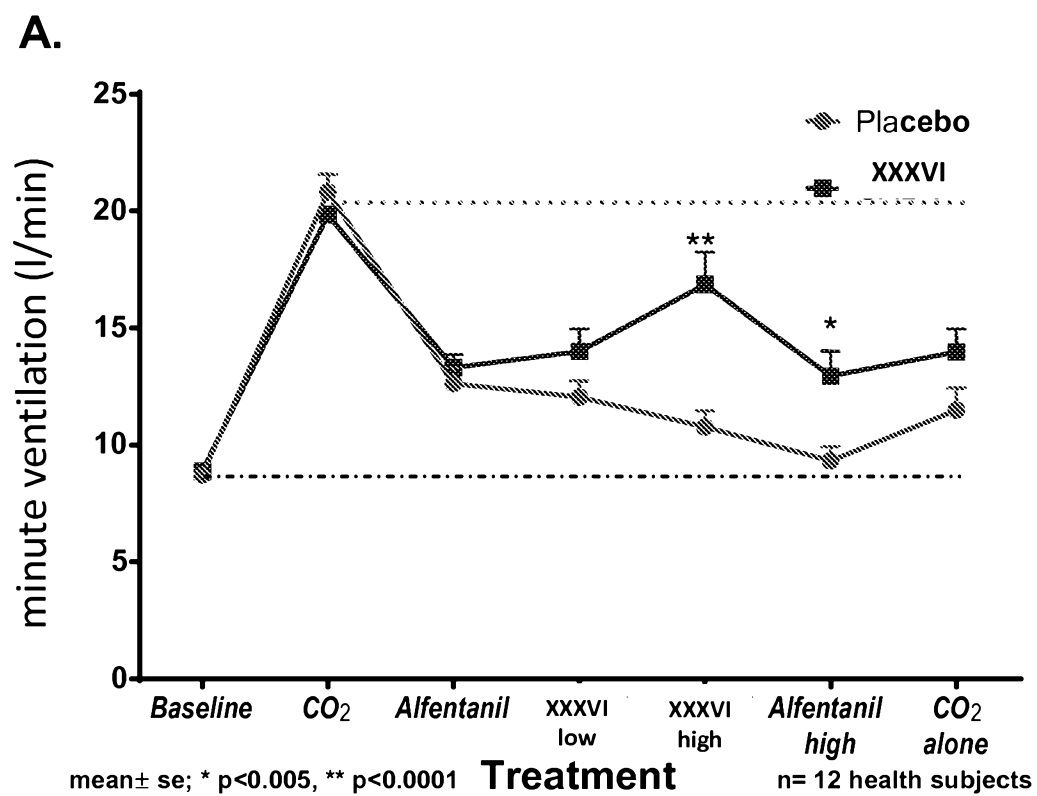
Fig. 41A

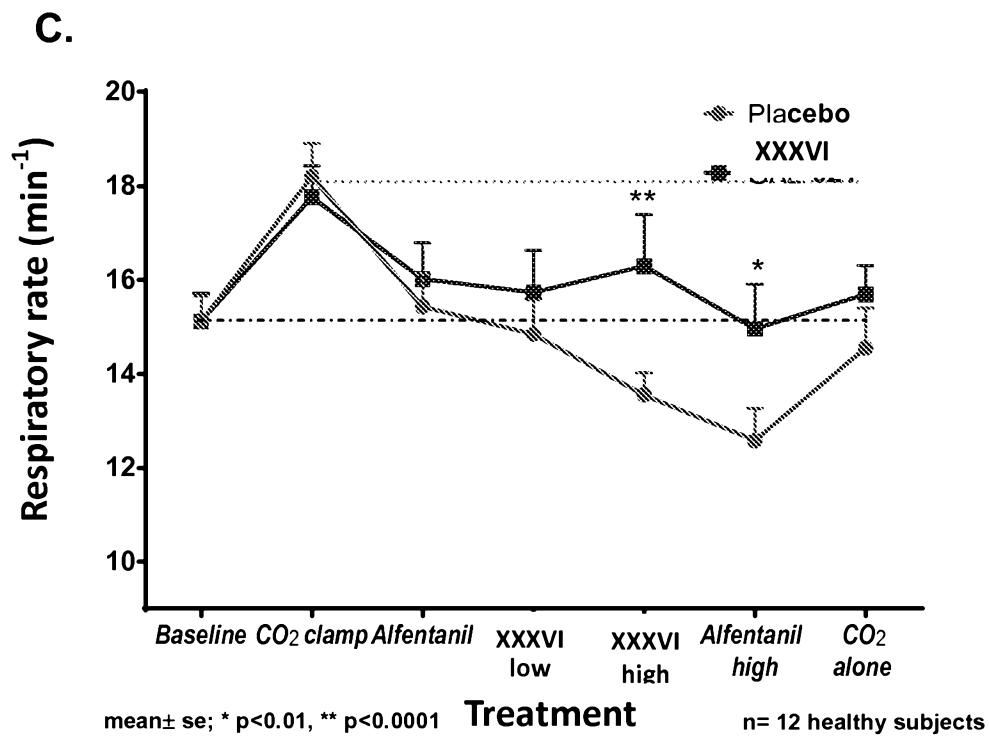
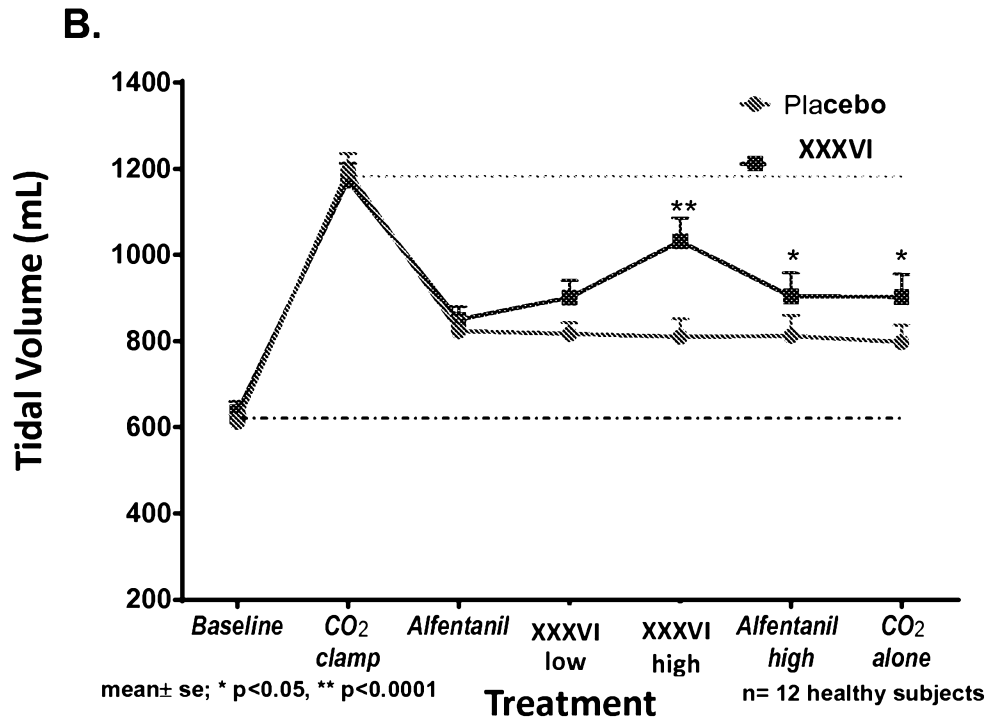
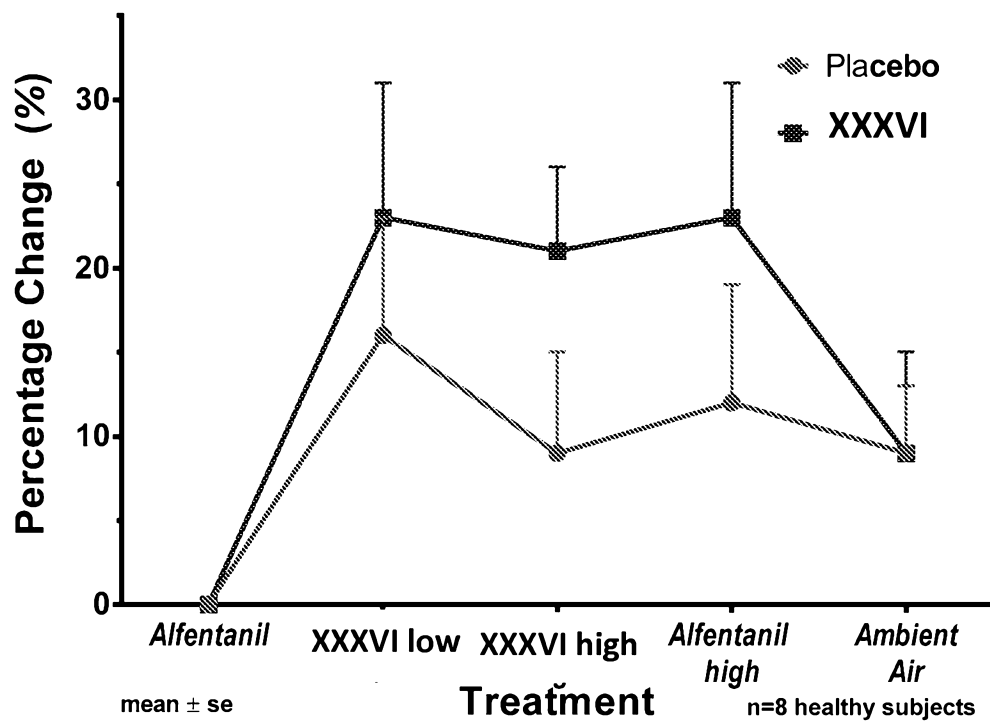
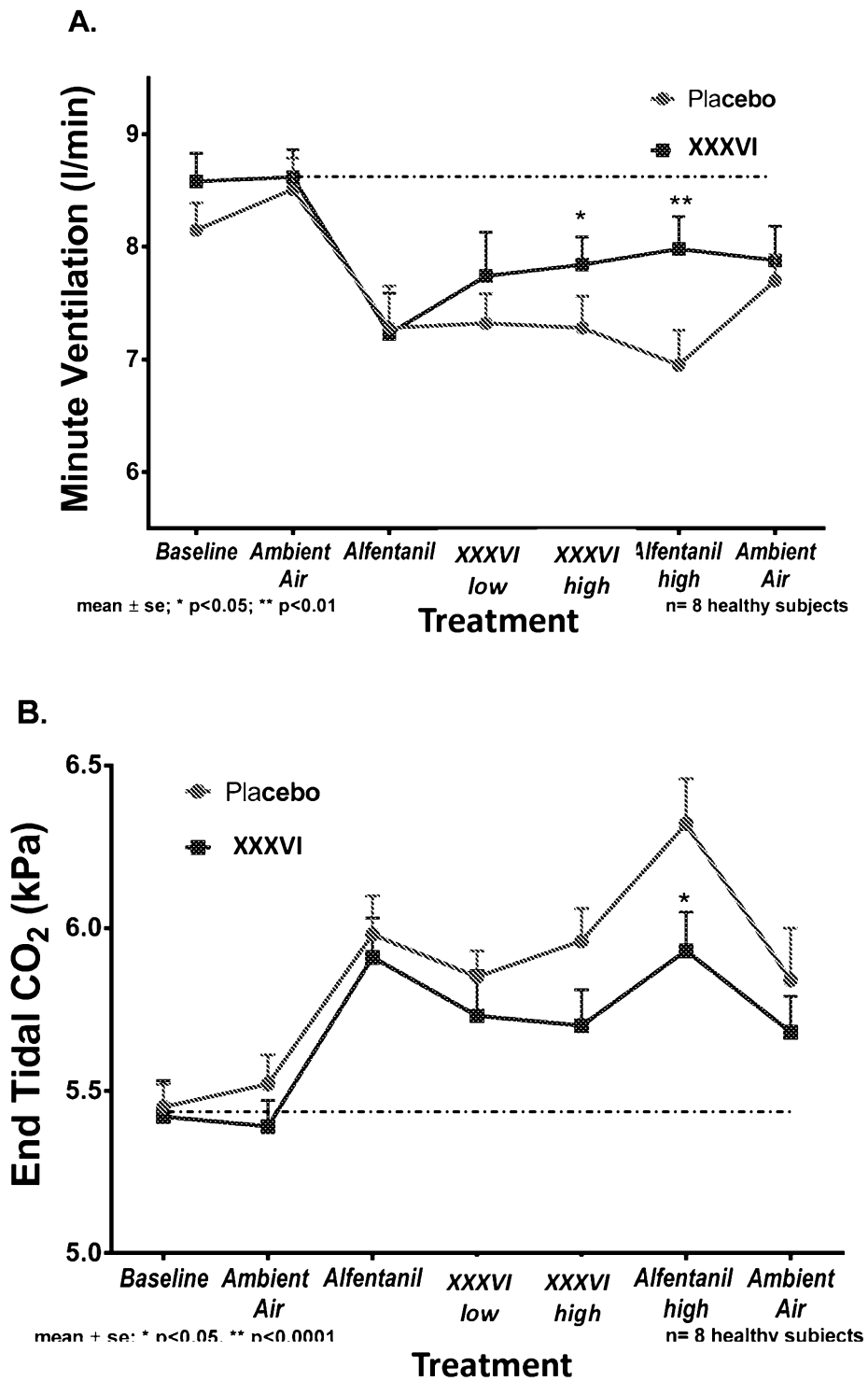
Fig. 41B-C

Fig. 42

Figs. 43A-B

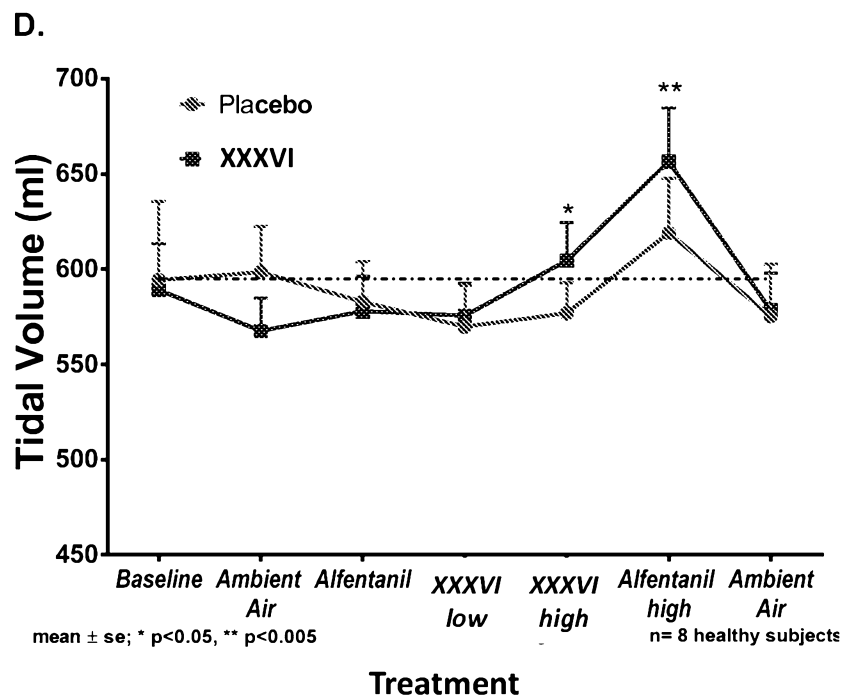
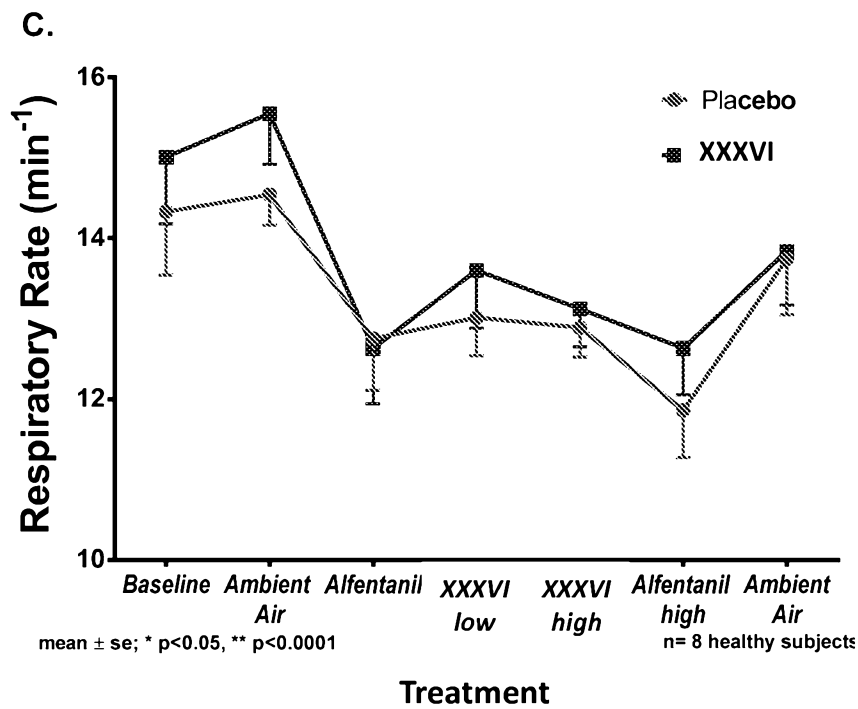
Figs. 43C-D

Fig. 44A

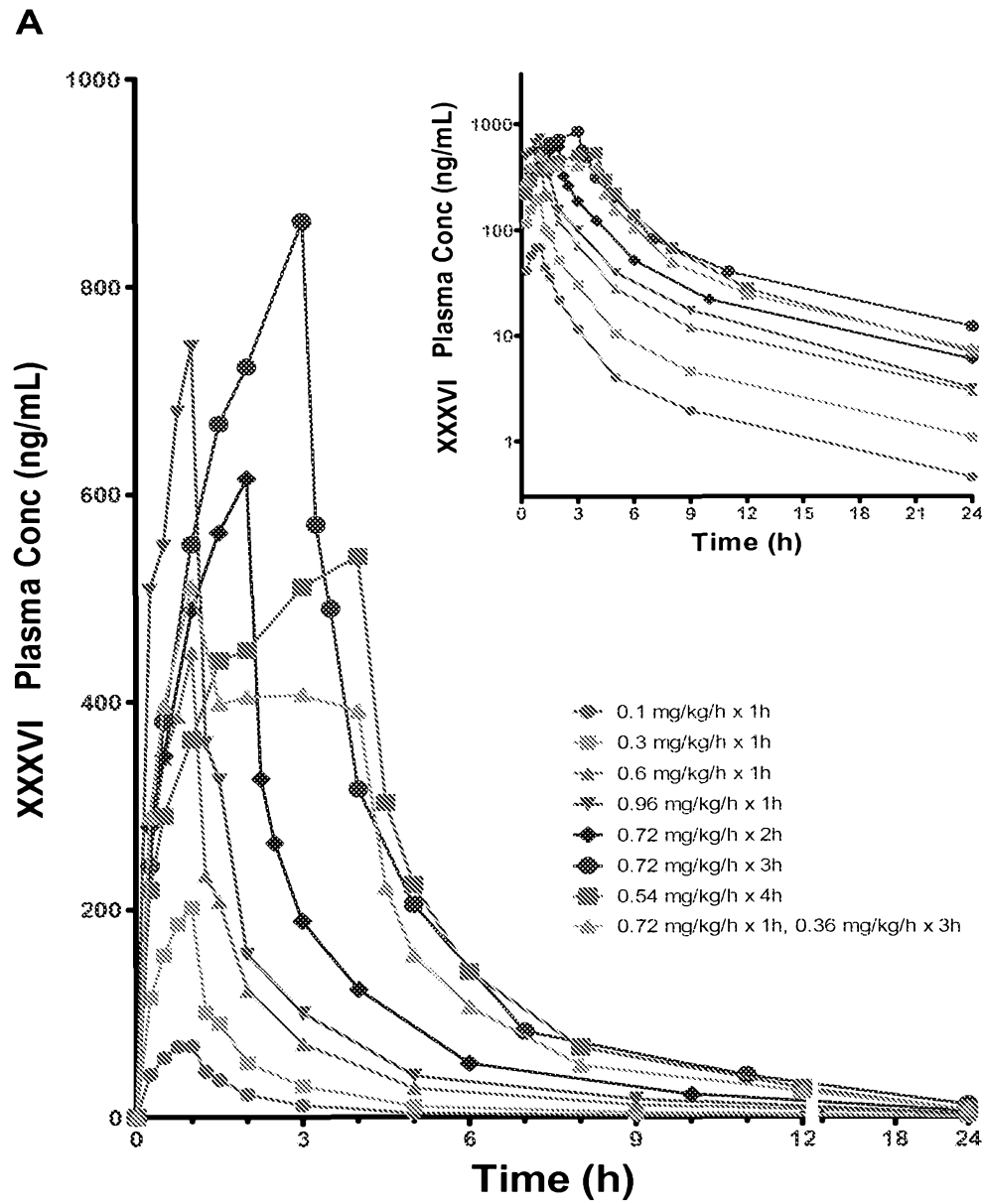


Fig. 44B